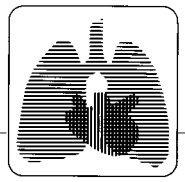

exercise and the heart

Clinical and Exercise Test Determinants of Survival After Cardiac Transplantation*

Jonathan Myers, PhD; Odd Geiran, MD, PhD; Svein Simonsen, MD, PhD; Afshin Ghuyoumi, MD; and Lars Gullestad, MD, PhD

Background: **Cardiac transplantation (CTX) is now a viable option for patients with end-stage heart failure, but there remains a paucity of available donor hearts relative to the demand for them. Establishing prognosis after CTX can help direct this resource to patients most likely to benefit, as well as to help guide therapy for CTX recipients. Clinical, exercise, and hemodynamic factors associated with survival after CTX have not been well established.**

Methods: **One hundred seventy-four randomly selected patients who underwent heart transplantation between 1983 and 1999 at Rikshospitalet University Hospital were included in the study. Data were collected as a part of routine posttransplantation management a mean of 3.5 ± 2.1 years (± SD) after CTX. Clinical, cardiopulmonary exercise testing, and hemodynamic measures were performed, including measures of peak oxygen uptake ($\dot{V}O_2$), ejection fraction, cardiac index, pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure, creatinine, and the presence of coronary artery disease. Patients were followed up for a mean of 7.1 ± 2.1 years; all-cause mortality was used as the end point for survival analysis.**

Results: **During the follow-up period, 39 patients died; the average annual mortality was 3.6%. Peak $\dot{V}O_2$ was 19.6 ± 5.6 mL/kg/min, representing 70.5 ± 6.7% of the age-predicted value. Only right atrial pressure and PCWP differed between those who survived and those who died; both were slightly higher among those who died. By Cox proportional hazard analysis, there were no age-adjusted univariate or multivariate predictors of survival among continuous variables. Exploring various cut points revealed that serum creatinine > 118 μmol/L, PCWP > 12 mm Hg, and mean pulmonary artery pressure > 25 mm Hg were significant univariate predictors of mortality. These cut points for PCWP and pulmonary artery pressure generated hazard ratios of 2.3 and 2.9, respectively.**

Conclusion: **Long-term survival after CTX was comparatively high in our cohort, with 5-year survival > 80%. Standard clinical, hemodynamic, and cardiopulmonary exercise test variables were not strong predictors of mortality in CTX patients a mean of 7 years after CTX. The association between elevated hemodynamic pressures and mortality, although weak, suggests that ventricular compliance, pulmonary vascular resistance, or both, may predict long-term survival after CTX.**

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Key words: cardiac transplantation; cardiopulmonary exercise testing; survival

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CTX = cardiac transplantation; EF = ejection fraction; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RER = respiratory exchange ratio; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen uptake

Cardiac transplantation (CTX) is now a widely accepted therapeutic option for patients with end-stage heart failure; overall 5-year survival is currently estimated to be 65 to 75%.[1] Although many advances have occurred in transplantation medicine over the last 2 decades, factors influencing short-term and long-term survival after CTX are not well defined. Several clinical challenges persist in regard to treatment of CTX recipients that influence their long-term survival. These include accelerated coronary atherosclerosis and associated complications,[2–5] infection,[5,6] and stability of ventricular function.[3]

Table 1—*Patient Characteristics With Univariate Comparison Between Those Who Died and Those Who Survived

Variables	Total (n = 175)	Survived (n = 135)	Died (n = 39)	p Value
Age, yr	52 ± 12	51 ± 12	53 ± 11	0.30
Height, cm	177 ± 7	177 ± 7	177 ± 6	0.81
Weight, kg	80 ± 13	79 ± 13	80 ± 13	0.68
BMI	25.4 ± 3.7	25.4 ± 3.7	25.6 ± 3.6	0.75
Follow-up, yr	7.1 ± 2.1	6.7 ± 2	8.3 ± 1.7	< 0.001
Resting HR, beats/min	96 ± 16 (n = 141)	94 ± 17	100 ± 14	0.07
Maximal HR, beats/min	147 ± 22	146 ± 22	150 ± 20	0.27
Maximal systolic BP, mm Hg	191 ± 31 (n = 150)	191 ± 31	191 ± 31	0.95
Maximal diastolic BP, mm Hg	93 ± 16 (n = 149)	93 ± 17	96 ± 15	0.40
Maximal $\dot{V}O_2$, L/min	1.5 ± 0.48	1.6 ± 0.5	1.5 ± 0.4	0.29
Maximal RER	1.19 ± 0.14	1.19 ± 0.14	1.18 ± 0.12	0.72
Maximal $\dot{V}E$, L/min	65.6 ± 19.7	65.9 ± 20.1	64.8 ± 18.4	0.78
% age-predicted $\dot{V}O_2$	70.5 ± 16.7	70.8 ± 17.5	69.8 ± 13.7	0.75
Peak W	135.5 ± 43.5	137.6 ± 43.6	128.8 ± 43.6	0.27
LVEDP, mm Hg	11.6 ± 5.6 (n = 135)	11.4 ± 5.2	12.5 ± 6.7	0.33
EF, %	72.1 ± 18.9 (n = 130)	70.8 ± 20.4	76.8 ± 11.7	0.13
Creatinine, μmol/L	125 ± 39 (n = 145)	123 ± 37	134 ± 43	0.14
RAP, mm Hg	4.7 ± 3.2 (n = 157)	4.6 ± 3.1	5.3 ± 3.8	0.29
MPAP, mm Hg	17.4 ± 5.5 (n = 160)	16.9 ± 5.3	19.2 ± 5.7	0.03
a-$\dot{V}O_2$ difference	48.6 ± 12.1 (n = 159)	48.7 ± 12.3	48.1 ± 12	0.77
PCWP, mm Hg	9.2 ± 4.6 (n = 160)	8.9 ± 4.4	10.6 ± 5.2	0.05
Cardiac index, L/min	2.63 ± 0.60 (n = 160)	2.64 ± 0.61	2.59 ± 0.58	0.63
TxCAD, %	69 (n = 155)	72	62	0.09
Cardiac output, L/min	5.2 ± 1.2 (n = 160)	5.2 ± 1.2	5.1 ± 1.1	0.65
pANP, mmol/L	1,729 ± 1,195 (n = 102)	1,713 ± 1,117	1,677 ± 1,425	0.90
CYA dose, mmol/L	237 ± 70	238 ± 73	232 ± 60	0.61

*Data are presented as mean ± SD unless otherwise indicated. a-$\dot{V}O_2$ difference = arterial-venous O_2 difference; pANP = end terminal atrial natriuretic peptide; TxCAD = presence of CAD; CYA dose = cyclosporine-A dose.

The knowledge that particular clinical, hemodynamic, exercise, or neuroendocrine variables unique to CTX patients may be associated with survival is useful, in that it helps to direct therapy and optimize prognosis. In addition, further defining donor and recipient characteristics that predict outcomes after CTX helps to direct scarce donor hearts to patients who are most likely to benefit.

In recent years, the exercise test has been increasingly recognized for its value in stratifying risk in patients with cardiovascular disease.[7,8] Specifically, exercise capacity expressed as peak oxygen uptake ($\dot{V}O_2$) has become an important factor in selecting or listing patients with chronic heart failure for CTX.[9] Less is known, however, about factors associated with risk after CTX; few data are available on the association between clinical and exercise test responses and survival after CTX. Moreover, previous studies have tended to be small, and there have been few integrated approaches that have included relevant demographic, clinical, hemodynamic, and exercise data. The purposes of the present study were as follows: (1) to characterize the exercise response of patients after CTX; and (2) to address the relation between clinical, hemodynamic, and exercise test variables and survival among CTX patients evaluated over a 12-year period.

Materials and Methods

Patients

One hundred seventy-four patients who underwent heart transplantation between 1983 and 2001 at Rikshospitalet University Hospital, Oslo were included in the study. The Regional Ethics Committee approved the study, and informed consent was obtained. Data were collected as a part of routine posttransplantation management, which included maximal exercise testing and hemodynamic assessment. The indication for CTX was coronary artery disease (CAD) in 57%, idiopathic dilated cardiomyopathy in 37%, and other indications in 6%. Clinical characteristics of the patients are presented in Table 1. All patients were in clinically stable condition with no history of recent rejection or concurrent

*From the Division of Heart and Lung Diseases (Drs. Geiran, Simonsen, and Gullestad), Rikshopitalet, Oslo, Norway; and the Cardiology Division (Drs. Myers and Ghuyoumi), Palo Alto Veterans Affairs Health Care System, Palo Alto, CA.
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Correspondence to: Jonathan Myers, PhD, Palo Alto Veterans Affairs Health Care System, Cardiology Division – 111C, 3801 Miranda Ave, Palo Alto, CA 94304

illness. All were receiving standard triple-drug maintenance immunosuppressive therapy with cyclosporine A, azathioprine, and prednisolone. At the time of the exercise test, none were treated with negative inotropic agents (beta-blockers, diltiazem, or verapamil).

Hemodynamic Assessment

Standard left-sided cardiac catheterization was performed. Left ventricular end-diastolic pressure (LVEDP) was recorded and left ventricular ejection fraction (EF) was obtained from angiographic ventriculography. Hemodynamic data were obtained from catheterization performed after right ventricular endomyocardial biopsies. Pressures included right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), and pulmonary capillary wedge pressure (PCWP). Cardiac output was determined by thermodilution or the Fick equation.

Exercise Testing

All patients were familiar with the test procedure. Maximal, upright, symptom-limited (general or leg fatigue, shortness of breath, or lightheadedness) exercise testing was performed using an electrically braked bicycle ergometer. The test employed an individualized stepwise protocol, with a starting load of 20 to 50 W, increasing by 20 to 50 W every second minute until exhaustion (defined as an inability to keep the pedaling rate steady at 60 revolutions per minute). Simultaneous gas exchange and hemodynamic monitoring were performed. Ventilatory $\dot{V}O_2$ was measured using the EOS/SPRINT system (E. Jaeger, GmbH CoKG; Wurzburg, Germany). Gas exchange data were measured with a mixing chamber and recorded every 30 s. $\dot{V}O_2$, carbon dioxide output, minute ventilation ($\dot{V}E$), and respiratory exchange ratio (RER) were calculated on-line. Peak $\dot{V}O_2$ was defined as the highest $\dot{V}O_2$ achieved during exercise. Age-predicted values for peak $\dot{V}O_2$ were calculated according to the equation of Wasserman et al.[10] Heart rate (HR) was recorded continuously from an ECG, and BP was measured noninvasively with an automatic BP recorder before exercise, during exercise, and throughout the recovery period. Subjective perception of fatigue (Borg scale)[11] was recorded at the end of each exercise stage and at maximal exercise.

Statistical Analysis

NCSS software (Salt Lake City, UT) was used for all statistical analyses. All results are expressed as mean ± SD. Differences in mean values between patients who survived and those who died were assessed using unpaired *t* tests. Overall mortality was the end point used for survival analysis. A Cox proportional hazards model was used to determine which variables were independently and significantly associated with time to death. Kaplan-Meier curves were used to assess survival using hemodynamic data at various cut points. The survival analysis was adjusted for age in single years as a continuous variable.

Results

The mean follow-up period was 7.1 ± 2.1 years, and the average annual mortality was 3.6%. The mean duration between CTX and evaluation for the current study was 3.5 ± 2.1 years. During the follow-up period, there were 39 deaths from all causes. The most common reason for stopping exercise was leg fatigue (69.8%), followed by dyspnea (16.9%) and general fatigue (11.6%). Mean peak $\dot{V}O_2$ was 19.4 ± 0.4 mL/kg/min, representing 70.5% of the age-predicted value.[10] Demographic, exercise, clinical, and hemodynamic characteristics in the total group and among those who survived and those who died are presented in Table 1. Only PCWP (8.9 ± 4.4 mm Hg vs 10.6 ± 5.2 mm Hg, $p < 0.05$) and MPAP (16.9 ± 5.3 mm Hg vs 19.2 ± 5.7 mm Hg, $p < 0.05$) differed between groups; the higher values were observed among those who died. The Cox proportional hazards model revealed that there were no significant age-adjusted multivariate predictors of mortality. Age-adjusted univariate clinical, hemodynamic, and exercise test predictors of mortality are presented in Table 2. When all data were expressed as continuous variables, there were no significant predictors of mortality. An exploratory analysis of various cut points demonstrated that a creatinine level > 118 μmol/L, PCWP > 12 mm Hg, and MPAP > 25 mm Hg significantly predicted mortality. Figure 1 illustrates a Kaplan-Meier survival curve among patients with resting PCWPs ≤ 12 mm Hg and > 12 mm Hg; 5-year survival was 90% vs 60% among those with resting PCWPs ≤ 12 mm Hg vs > 12 mm Hg, respectively ($p < 0.01$).

Discussion

Exercise Test Responses in CTX Patients

Exercise capacity of the current patients was typical of CTX recipients, in that mean peak $\dot{V}O_2$ was 19.5 mL/kg/min. Although we did not have peak $\dot{V}O_2$ values before CTX, this is substantially higher than typical groups of patients with congestive heart failure (CHF) who are considered for transplantation, in which mean peak $\dot{V}O_2$ typically ranges from 10 to 12 mL/kg/min.[9,12] However, the post-CTX peak $\dot{V}O_2$ represents only 70% of the age-predicted value, confirming the fact that exercise capacity remains markedly reduced relative to individuals with intact hearts of similar age.[13–15] Resting HR was high (97 beats/min) and peak HR was limited (147 beats/min), consistent with an impaired chronotropic response to exercise. The limited range within which HR increased (50 beats/min) likely contributed to limiting cardiac output and thus peak $\dot{V}O_2$. A number of other factors have been proposed in order to explain reduced exercise tolerance after CTX, including hemodynamic effects of immunosuppressive therapy, abnormal skeletal muscle metabolism and strength, decreased capillary density, and deconditioning.[13,16–19]

Table 2—*Age-Adjusted Univariate Predictors of Mortality

Variables	Mean	Regression Coefficient	SE	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit	p Value
Donor age, yr	28.9 ± 10.4	− 0.02	0.02	0.98	0.95	1.01	0.27
BMI	25.4 ± 3.7	0.02	0.05	1.02	0.94	1.12	0.61
HR supine, beats/min	96 ± 16 (n = 141)	0.01	0.02	1.01	0.98	1.05	0.50
HR sit, beats/min	101 ± 17	0.01	0.01	1.01	1.00	1.03	0.14
Maximum HR, beats/min	147 ± 22	0.01	0.01	1.01	0.99	1.03	0.27
Systolic BP rest, mm Hg	134 ± 21	− 0.01	0.01	0.99	0.98	1.01	0.50
Maximum systolic BP, mm Hg	191 ± 31 (n = 150)	− 0.003	0.01	1.00	0.99	1.01	0.61
Maximum diastolic BP, mm Hg	93 ± 16 (n = 149)	0.003	0.01	1.00	0.98	1.03	0.78
Maximum $\dot{V}O_2$, L/min	19.6 ± 5.6	− 0.03	0.04	0.97	0.90	1.04	0.43
Maximum RER	1.19 ± 0.14	− 0.54	1.24	0.58	0.05	6.65	0.66
Maximum $\dot{V}E$, L/min	65.6 ± 19.7	0.0003	0.01	1.00	0.98	1.02	0.97
% Age predicted $\dot{V}O_2$, L/min	70.5 ± 16.7	− 0.01	0.01	0.99	0.98	1.01	0.60
Peak W	135.5 ± 43.5	− 0.002	0.004	1.00	0.99	1.01	0.59
LVEDP, mm Hg	11.6 ± 5.6 (n = 135)	0.02	0.03	1.02	0.96	1.09	0.49
EF, %	72.1 ± 18.9 (n = 130)	0.02	0.01	1.02	1.00	1.05	0.10
Creatinine, μmol/L	125 ± 39 (n = 145)	0.01	0.02	1.01	0.98	1.05	0.46
RAP, mm Hg	5.3 ± 8.2 (n = 157)	0.02	0.01	1.02	1.00	1.04	0.11
MPAP, mm Hg	17.4 ± 5.5 (n = 160)	0.06	0.03	1.06	1.00	1.12	0.06
a-$\dot{V}O_2$ difference	48.6 ± 12.1 (n = 159)	− 0.01	0.02	0.99	0.96	1.02	0.61
PCWP, mm Hg	9.2 ± 4.6 (n = 160)	0.05	0.03	1.05	0.99	1.12	0.13
Cardiac index, L/min	2.64 ± 0.56 (n = 159)	− 0.13	0.33	0.88	0.46	1.67	0.69
CAD, %	69 (n = 155)	− 0.34	0.37	0.71	0.34	1.46	0.35
Cardiac output, L/min	5.2 ± 1.2 (n = 160)	− 0.003	0.14	1.00	0.75	1.32	0.98
pANP, mmol/L	1,729 ± 1,195 (n = 102)	− 0.00004	0.0002	1.00	1.00	1.00	0.85
CYA dose, mmol/L	237 ± 70	− 0.00005	0.003	1.00	0.99	1.01	0.99
Creatinine > 118, μmol/L		0.38	0.36	1.47	1.44	4.34	0.03
PCWP > 12 mm Hg		0.84	0.35	2.33	1.18	4.59	0.01
MPAP > 25 mm Hg		1.05	0.45	2.87	1.18	6.96	0.02

*See Table 1 for expansion of abbreviations not used in text.

Survival

The survival rate we observed (3.6% annual mortality rate) is similar to, or slightly better than, other studies in the current treatment era. The fact that we did not observe any clinical, exercise, or hemodynamic variables to be multivariate predictors of mortality underscores the fact that predicting survival in CTX patients is more complex than other cardiovascular conditions. This is likely due to the many mitigating factors associated with CTX, such as comorbidities and problems related to rejection.[5,6] In our proportional hazard analysis, we attempted to include factors previously shown to be markers of risk in CTX recipients, such as recipient CAD, donor and recipient age, and EF,[2,3,5,6] as well as hemodynamic and exercise test variables known to predict mortality in patients with CHF, *eg*, peak $\dot{V}O_2$, percentage of age-predicted peak $\dot{V}O_2$ achieved, cardiac output, EF, and atrial natriuretic peptide.[9,12,20,21] Our findings are consistent with the observations of Fraund et al,[5] in which CTX patients who survived > 10 years were compared to those who survived ≤ 10 years. There were no independent predictors of long-term survival by either univariate analysis or multivariate logistic regression, and no significant differences in donor or recipient characteristics between survivors and nonsurvivors. Although limited evidence suggests that factors such as accelerated CAD, donor age, and ventricular function are associated with outcomes following CTX,[2–4] we did not find any of these factors to be associated with all-cause mortality.

The variables we observed that were associated with mortality were limited to elevated creatinine, and resting hemodynamic pressures at particular cut points (PCWP > 12 mm Hg and MPAP > 25 mm Hg). Several caveats should be noted in considering these findings. First, none of these variables were significant by multivariate analysis, suggesting that none has an independent association with mortality. Second, they were found to be univariately significant only after an exploratory analysis, and only using relatively high cut points. Nevertheless, these variables generated considerable hazard ratios, ranging between 2.3 and 2.9. PCWP, for example, demonstrated marked differences in 5-year survival rates using the cut point ≤ 12 mm Hg vs > 12 mm Hg (90% vs 60% survival, $p < 0.01$; Fig 1).

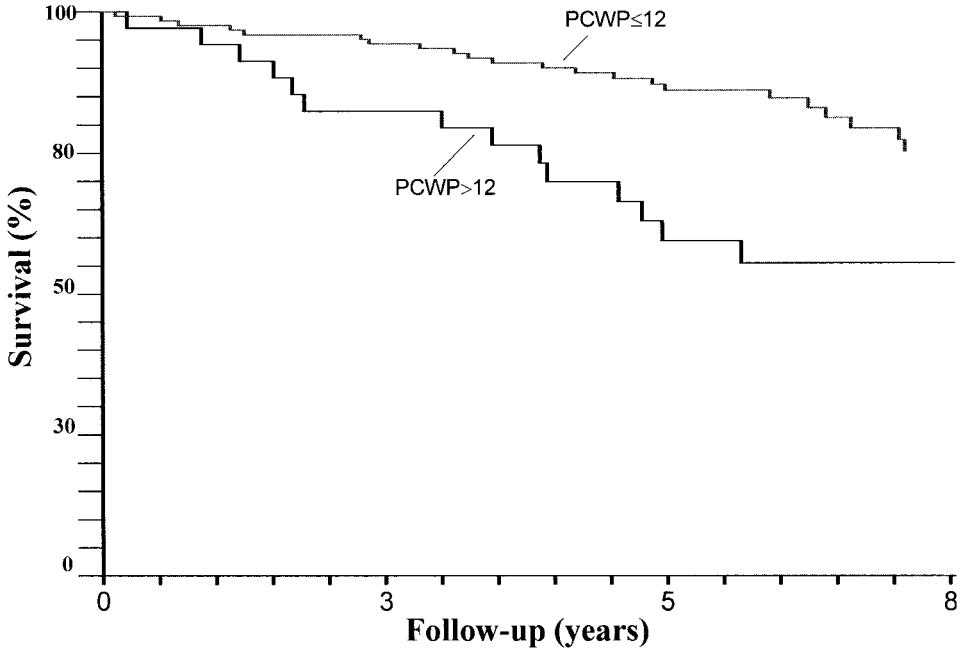

FIGURE 1. Survival curves for subjects stratified by PCWP ≤ 12 mm Hg and PCWP > 12 mm Hg ($p < 0.01$).

The hemodynamic pressure data raise the possibility that elevated cardiac filling pressures, possibly associated with poor ventricular compliance, increased pulmonary vascular resistance, or both, might contribute to reduced cardiac function and therefore survival. However, since these variables were not strong independent determinants of survival in our study, a larger data set may be required to confirm the role of hemodynamic data in predicting survival in CTX recipients. In terms of creatinine, it has been demonstrated renal insufficiency is one factor associated with poor outcomes in CHF and following CTX.[22,23] Elevated creatinine level may reflect an early indication of renal insufficiency, a surrogate for worsening of cardiac function, or a marker of comorbid disease. Again, however, the creatinine level > 118 mg/dL was observed to be associated with mortality in our study only after an exploratory analysis, and was not a multivariate predictor of mortality.

Previous Studies

While exercise capacity and other exercise test variables are known to be among the most potent determinants of survival in patients with CHF,[9,12,20] the availability of such data are limited among CTX recipients. Verhoeven and colleagues[2] observed that the presence of perfusion abnormalities by stress ^{201}Tl imaging was the only multivariate predictor of survival among 47 patients followed up for 1 year after CTX. Barbir et al[3] assessed the prognostic role of noninvasive tests (exercise ECG, radionuclide ventriculography, and echocardiography) a mean of 2.1 years following CTX in 91 patients. Echocardiographic EF > 60% was the most important determinant of survival, followed by absence of significant angiographic coronary disease, whereas radionuclide ventriculography and exercise ECG were not significant predictors of survival; however, other exercise test variables, *eg*, exercise capacity, BP, and chronotropic responses, were not included in the analysis.

Limitations

We did not have cause of death among our patients. A better sense of the prognostic utility of clinical, exercise, and hemodynamic data specifically in CTX patients may have been obtained were we able to determine cardiovascular and noncardiovascular death. Although the present study was one of the largest to our knowledge to assess clinical and exercise variables in the context of prognosis in CTX, our sample size was nevertheless relatively small. We were only able to code post-CTX coronary disease as present or absent, and did not have any additional details on the degree of CAD. Lastly, with the exception of donor age, we did not have detailed information on risk factors among donors.

SUMMARY

Long-term survival was comparatively high in our sample, with 5-year survival > 80%. Standard clini-

cal and exercise variables poorly predict mortality in patients evaluated a mean of 3.5 years after CTX and followed up for 7 years. Heightened hemodynamic pressures (PCWP and pulmonary artery pressures) and elevated creatinine are potentially important determinants of mortality in CTX patients, though we found these variables predicted mortality only by univariate analysis and only at relatively high cut points. Nevertheless, these findings suggest that renal function, ventricular compliance, pulmonary vascular resistance, or all three have a role in long-term outcomes among patients after CTX.

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