Cytomegalovirus Serostatus as Predictor for Adverse Events After Cardiac Surgery: A Prospective Observational Study

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Objective: **To clarify whether reactivated cytomegalovirus (CMV) infections in critically ill patients lead to worse outcome or just identify more severely ill patients. If CMV has a pathogenic role, latently infected (CMV-seropositive) patients should have worse outcome than seronegative patients because only seropositive patients can experience a CMV reactivation.**

Design: **Post-hoc analysis of a prospective observational study.**

Setting: **Single university hospital.**

Participants: **The study comprised 983 consecutive patients scheduled for on-pump surgery.**

Interventions: **None.**

Measurements and Main Results: **CMV antibodies were analyzed in preoperative plasma samples. Postoperative adverse events (reintubation, low cardiac output or reinfarction, dialysis, stroke) and 30-day and 1-year mortality were evaluated prospectively. The plasma of reintubated patients and matched control patients was tested for CMV deoxyribonucleic acid, and 618 patients were found to be seropositive for CMV (63%). Among these, the risk for reintubation was increased (10% *v* 4%, p = 0.001). This increase remained significant after correction for confounding factors (odds ratio 2.70, p = 0.003) and was detectable from the third postoperative day throughout the whole postoperative period. Other outcome parameters were not different. Reintubated seropositive patients were more frequently CMV deoxyribonucleic acid-positive than were matched control patients (40% *v* 8%, p < 0.001).**

Conclusions: **CMV-seropositive patients had an increased risk of reintubation after cardiac surgery, which was associated with reactivations of their CMV infections. Additional studies should determine whether this complication may be prevented by monitoring of latently infected patients and administering antiviral treatment for reactivated CMV infections.**

KEY WORDS: cardiac surgery, adverse events, reintubation, cytomegalovirus serostatus, latent cytomegalovirus infection, cytomegalovirus deoxyribonucleic acid

HUMAN CYTOMEGALOVIRUS (CMV) causes mostly asymptomatic or mild mononucleosis-like infections in immunocompetent patients,[1] with a seroprevalence of between 40% and 100% in adult populations.[2] Primary CMV infection leads to lifelong latency of CMV with possible reactivations, especially in immunocompromised patients. CMV latency can be recognized by detection of IgG antibodies against CMV in plasma (seropositive patients), whereas patients without CMV antibodies (seronegative patients) are believed never to have been infected.

Even in nonimmunosuppressed patients in intensive care units (ICU), active CMV infections have been detected frequently, with most infections presumably being reactivations of latent CMV infections.[3] Patients with active CMV infection have demonstrated significantly increased morbidity and mortality.[4] Whether the reactivation of latent CMV infections aggravates these patients' symptoms and prognosis or whether active CMV infections simply indicate a subpopulation of more severely ill patients not identified by other variables is not known.[3,5]

If a cause-effect relationship between active CMV infections and inferior outcome exists, latently infected (seropositive) patients should have an increased morbidity compared with noninfected (seronegative) patients because only seropositive patients develop active CMV infections.[4] If, on the other hand, active CMV infections simply indicate a more severely ill subgroup of patients, the outcome should not be influenced by the CMV serostatus.

This study aimed to determine the influence of preoperative CMV serostatus on postoperative outcomes in cardiac surgery patients.

METHODS

Patients

This was a secondary analysis of a large prospective, observational trial primarily aimed to determine the relationship between preoperative cerebral oxygen saturation (ScO_2) and clinical outcomes in patients undergoing cardiac surgery. The dataset has been used for multiple analyses, and the details of recruitment and consent have been presented elsewhere.[6,7]

Briefly, all patients scheduled for cardiac surgery with cardiopulmonary bypass (CPB) at the University of Lübeck from January 1 to December 31, 2008, were screened for participation in the prospective, observational trial. Exclusion criteria were age younger than 18 years and planned off-pump surgery.

Of 1,178 patients included in the original study, 195 patients could not be evaluated for the analysis presented here because

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aliquots were not available from the preoperatively drawn plasma samples for 190 patients. The true serostatus could not be determined in 5 patients because blood transfusions had been given before the first plasma sample was drawn, making it impossible to exclude passive antibody transfer via blood transfusions as cause for seropositive test results. In total, 983 patients were eligible for this secondary analysis.

Ethics Approval and Consent to Participate

The study was approved by the local ethical committee (Ethikkommission der Universität zu Lübeck, Lübeck, Germany) under the reference number 07-146. The examination of stored plasma samples for CMV DNA was approved by the same ethical committee under reference number 16-040. Written informed consent was obtained from all elective and urgent patients and emergency patients capable of communication. In cases of sedated or intubated patients scheduled for emergency surgery, consent was obtained from the next of kin and reconfirmed after recovery. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Standard Risk Factors and Clinical Outcomes

In addition to demographic variables serving as potential risk factors, the following specific cardiovascular risk factors were assessed: left ventricular ejection fraction (LVEF), New York Heart Association grade, additive EuroSCORE, and estimated glomerular filtration rate. LVEF was derived from the preoperative diagnostics (levocardiography or echocardiography) and graded as follows: severely reduced (LVEF less than 30%), moderately reduced (30%-49%), and normal (50% or more). The additive EuroSCORE was calculated according to Roques et al[8] and analyzed as a continuous variable. The estimated glomerular filtration rate was calculated from preoperative plasma creatinine using the abbreviated Modifications of Diet in Renal Disease equation.[9] Clinical outcomes (30-day mortality, major complications, and duration of treatment in the high-dependency unit [HDU]) were derived from the prospectively sampled cardiac surgery database. All-cause 1-year mortality was determined from the hospital database or by contacting the patient's primary physician, the patient, or the patient's next of kin. The follow-up rate was 98.3%.

Determination of CMV Serostatus

Arterial blood samples were obtained immediately before induction of anesthesia. Ethylenediaminetetraacetic acid plasma was separated and stored at –80C° for further analysis. IgG antibodies against CMV were determined out of these samples using a chemiluminescent microparticle immunoassay against AD169-coated microparticles (Architect Anti-CMV IgG Assay; Abbott GmbH & Co. KG, Wiesbaden, Germany). The test was performed and evaluated according to the recommendations of the manufacturer. Samples with at least 6 arbitrary units of CMV antibodies per milliliter were considered seropositive. The assay has a sensitivity of 99.70% and a specificity of 99.69%.[10]

Determination of Active CMV Infection

For the determination of CMV DNA, aliquots of plasma samples sent to the blood bank for red blood cell crossmatching were used. At the authors' institution, these aliquots are stored routinely at –30°C to facilitate exclusion of presumed transmission of infectious diseases via blood transfusions (eg, acquired immunodeficiency syndrome or hepatitis). After expiration of the storage period necessary for look-back studies, all samples of the study cohort (reintubated patients and matched control patients) were tested. For each CMV-seropositive patient with reintubation, a control patient matched for age, sex, and all parameters associated with an elevated risk for reintubation was selected (Table 1).

DNA from 300-μL aliquots of plasma samples was extracted and tested for CMV DNA in duplicate using a highly sensitive TaqMan polymerase chain reaction with a detection limit of 12 international units of CMV DNA per milliliter, as described elsewhere.[11] Samples with invalid internal control or diverging results were retested twice. Active CMV infection was diagnosed by positive results for CMV DNA in at least 1 sample.

Anesthesia

General anesthesia was induced with etomidate and sufentanil and maintained with sevoflurane and remifentanil before and after CPB and with propofol and remifentanil during CPB. If necessary, midazolam was added to achieve the desired anesthesia depth. In addition to standard anesthesia monitoring, including electrocardiogram, invasive arterial blood pressure, central venous pressure monitoring, and monitoring of the depth of anesthesia with bispectral index (BIS Brain Monitoring System; Covidien, Minneapolis, MN), intraoperatively all patients were equipped routinely and bihemispherically with ScO_2 sensors (INVOS Cerebral Oximeter 5100; Covidien).

CPB Management

Before CPB, all patients received 400 IU/kg of heparin. Surgery was performed with the patient in moderate hypothermia using antegrade blood cardioplegia. Blood flow during CPB was adjusted to achieve a mean arterial blood pressure between 50-to-70 mmHg, a mixed venous oxygen saturation—measured at the inflow of the CBP circuit—greater than 70%, and relative ScO_2 concentrations more than 80% of the preoperative baseline, determined in the operating room with the patient breathing room air. To achieve this goal,

Table 1. Risk Factors for Postoperative Reintubation

	p Value	Odds Ratio
Surgical priority: <12 hours and emergency	<0.001	3.75 (1.91-7.34)
Body mass index, kg/m^2	0.001	0.89 (0.83-0.95)
CMV seropositive	0.003	2.70 (1.40-5.90)
Comorbidity: previous acute heart failure	0.004	2.54 (1.36-4.75)
Comorbidity: arterial hypertension	0.026	3.39 (1.16-9.97)

NOTE. Results of the logistic regression analysis (overall $p < 0.001$). American Society of Anesthesiologists grading; sex; type of surgery; preoperative therapy with amiodarone, intravenous nitrates, or direct vasodilators; or a history of angina pectoris or previous cardiac surgery had no significant influence ($p > 0.05$).