Delirium after Cardiac Surgery in Older Patients

Predictors of occurrence and outcome

Robert Jan Osse

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Delirium after Cardiac Surgery in Older Patients

Predictors of occurrence and outcome

Delirium na een hartoperatie bij oudere patiënten

Voorspellers van optreden en uitkomst

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CONTENTS

Chapter 1	Introduction	9
Chapter 2	Preoperative and operative predictors of delirium after cardiac surgery in elderly patients.	21
Chapter 3	Disturbed circadian motor activity patterns in postcardiotomy delirium.	35
Chapter 4	Screening methods for delirium: early diagnosis by means of objective quantification of motor activity patterns using wrist-actigraphy.	49
Chapter 5	High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults.	59
Chapter 6	Postoperative delirium in the long-term diminishes attention and executive functioning without affecting memory.	75
Chapter 7	General discussion and conclusions	91
Chapter 8	Summary	105
Chapter 9	Nederlandse samenvatting	111
Addendum	Author affiliations	121
	List of abbreviations	123
	List of publications	125
	Dankwoord	127
	Curriculum vitae	131

DER ERLKŌNIG.

J.W. von Goethe / F. Schubert

Wer reitet so spät durch Nacht und Wind?
Es ist der Vater mit seinem Kind;
Er hat den Knaben wohl in dem Arm,
Er faßt ihn sicher, er hält ihn warm.

„Mein Sohn, was birgst du so bang dein Gesicht?“
„Siehst, Vater, du den Erlkönig nicht?
Den Erlenkönig mit Kron’ und Schweif?“
„Mein Sohn, es ist ein Nebelstreif.“

„Du liebes Kind, komm, geh mit mir!
Gar schöne Spiele spiel ich mit dir;
Manch bunte Blumen sind an dem Strand,
Meine Mutter hat manch gülden Gewand.“

„Mein Vater, mein Vater, und hörest du nicht,
Was Erlenkönig mir leise verspricht?“
„Sei ruhig, bleibe ruhig, mein Kind;
In dürren Blättern säuselt der Wind.“

„Willst, feiner Knabe, du mit mir gehn?
Meine Töchter sollen dich warten schön;
Meine Töchter führen den nächtlichen Reihn,
Und wiegen und tanzen und singen dich ein.“

„Mein Vater, mein Vater, und siehst du nicht dort
Erlkönigs Töchter am düstern Ort?“
„Mein Sohn, mein Sohn, ich seh es genau;
Es scheinen die alten Weiden so grau.“

„Ich liebe dich, mich reizt deine schöne Gestalt;
Und bist du nicht willig, so brauch ich Gewalt.“
„Mein Vater, mein Vater, jetzt faßt er mich an!
Erlkönig hat mir ein Leids getan!“

Dem Vater grausets, er reitet geschwind,
Er hält in Armen das ächzende Kind,
Erreicht den Hof mit Müh‘ und Not;
In seinen Armen das Kind war tot.

Chapter

1

Introduction

FORMER CONCEPTS OF DELIRIUM

As early as in Hippocrates' medical writings, clinical pictures of patients experiencing delirium were described [1]. The syndrome we currently refer to as delirium was originally based on two distinct syndromes. A syndrome called *Phrenitis*, in which patients showed cognitive disturbances, exited and restless behaviour, with disruption of sleep, and a syndrome called *Lethargus*, in which patients were somnolent, apathetic, listless and showed slow mentation. Although it was known that *Phrenitis* could change into *Lethargus*, and vice versa, it was not until the late eighteenth century that both terms were displaced by the single term delirium. There is some uncertainty whether the word 'delirium' is derived from the Greek word ληρος, meaning empty drivel [2], or from the Latin word for disturbance of mind, *deliratio* [1]. Even in ancient times it was known that the emergence of a delirium was a bad prognostic sign and often a herald of death, but the pathophysiology remained obscure.
Based on meticulous observations of patients, the German psychiatrist Bonhoeffer reported in 1910 that the presence of the symptom *clouding of consciousness* could discriminate organic-psychiatric disorders from functional or endogenous psychiatric disorders [3]. Furthermore, he postulated that toxic substances originating from disease processes in the body or brain might cause delirium. A theory that is remarkably similar to the present-day inflammatory delirium theory, in which cytokines produced by glia cells induce delirium [4].
Engel and Romano in 1959 further elaborated on the delirium concept by describing the association between a reduced level of consciousness and the degree of slowing of the electro-encephalogram (EEG) [5]. Combined with the finding that slowing of the EEG was associated with derangements of cerebral metabolism, this provided additional evidence that delirium should be regarded as a syndrome of cerebral insufficiency.
Currently, delirium is the most frequently occurring organic-psychiatric syndrome in the general hospital. The incidence of delirium in the general hospital ranges from 5 to 32% [1,6], but in specific populations, such as older patients (aged 65 years or more) or patients in the intensive care unit (ICU), the incidence of delirium can be much higher [6-8].

DIAGNOSIS OF DELIRIUM

According to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV-TR) [9] delirium is defined by: A. Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention, B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia, C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day, and D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

Especially the fluctuating reduced level of consciousness, defined as 'impaired level of awareness of self and surroundings', is considered pathognomonic for delirium because it distinguishes delirium from (nearly) all other psychiatric disorders [1,3,5]. In delirium, all cognitive functions can be disturbed leading to a variety of symptoms including disorientation in time, place or person, difficulties in focusing, sustaining or shifting attention, impairment of memory, language disturbances, dyscalculia, visuo-constructive impairments, and impairment of directed thinking [1]. In addition, delusions, often with a paranoid content, hallucinations (mostly of the visual modality), emotional disturbances such as anxiety, irritability or anger, and sleep-wake cycle disturbances, can be present [1]. Psychomotor behaviour is often disturbed in which hyper- or hypoactivity and unpredictable fluctuations between these forms can be found. The hyperactive behaviour can cause dangerous clinical situations, i.e. a patient might fall out of bed, pull out intravenous lines or impair oxygen provision, whereas the hypoactive form may stay unrecognised, leading to misdiagnosis, delayed treatment, and malnutrition [10].

DELIRIUM AFTER CARDIAC SURGERY IN OLDER PATIENTS

In older patients (aged 65 years or more) undergoing cardiac surgery, the incidence of delirium is reported to range from 23 to 57% [11-13]. A range of medical conditions can lead to delirium in cardiac surgery patients, such as anaesthesia, inflammation, embolism, hypervolemia, hypotension, hypoxemia, cardiac dysrhythmias and infections. These possible precipitating conditions can occur in different combinations [14-16]. Especially patients with pre-existing cognitive dysfunction and older patients have a higher risk to experience a delirium after cardiac surgery [11,17].

Treatment of delirium according to the current guidelines [18,19] is based on treatment of predisposing and precipitating factors of delirium, providing adequate nursing care and a safe environment for the patient (psycho-hygienic measures), and drug treatment of delirium. The current treatment interventions have been proven effective [6,18-21] and prophylactic use of haloperidol has been effective to diminish the severity and duration of delirium in patients after hip surgery [22]. However, the effect of drug treatment for delirium was shown to be limited (e.g. insufficient to prevent delirium [22]) and drug treatment may be problematic due to safety issues [23]. Better understanding of the predictive pre-operative and operative factors for postoperative delirium in older patients undergoing cardiac surgery could provide more efficient ways to prevent delirium or to selectively use prophylactic drug treatment.

MOTOR ACTIVITY PATTERNS AND DELIRIUM

The distinction between the different motor-subtypes of delirium is often based on clinical ratings on item level of delirium rating scales (e.g. motor retardation or motor agitation in the Delirium Rating Scale –revised-98 (DRS-R98) [24] or by assessing the presence of specific symptoms according to the criteria of Liptzin and Levkoff [25]. Recently, two instruments to discern motor subtypes of delirium have been developed, the Delirium Motor Checklist (DMC) [26] and the Delirium Motor Subtype Scale (DMSS) [27]. These methods are, however, prone to selection bias, because especially hyperactive behaviour attracts the attention of the staff and, in contrast, longer periods of hypoactive, apathetic behaviour may pass unnoticed. As a consequence especially hypoactive or 'quiet' delirium, which is presumed to have the worst prognosis of the motoric subtypes, may stay unrecognised [10,28].

Wrist-actigraphy is an objective method to assess 24-h patterns of spontaneous motor activity for prolonged periods of time, which can accurately distinguish rest-activity patterns in a valid and reliable manner [29,30]. It has been used to quantify alterations of diurnal rest-activity patterns, disturbances in sleep-wake patterns, as well as psychomotor disturbances (psychomotor retardation or agitation) in a variety of (neuro)psychiatric (e.g. depression and dementia) patient categories [31-34]. Actigraphy was also used to analyse the motor activity patterns in a small sample of demented patients with a delirium [35], and to assess the depth of sedation and anaesthesia during surgery and recovery [36], but quantitative studies in delirium are lacking.

PATHOPHYSIOLOGICAL FACTORS OF DELIRIUM

Immune activation hypothesis

Because a variety of etiological factors can lead to the manifestation of a delirium, a final common pathophysiological pathway was postulated [4,6]. Immune activation, oxidative stress and cerebral neurotransmitter disturbances have been implicated in the pathogenesis of delirium. In various disease states, such as infection, tissue damage, hypoxia and atherosclerosis, the immune system is activated, causing monocytes and macrophages to produce cytokines and reactive oxygen species (ROS). In delirium, elevated levels of pro-inflammatory cytokines (including Tumor Necrosis Factor-α, Interleukin-1β, Interleukin-6 and Interleukin-8) have been found [37,38]. However, other studies failed to replicate these findings [39,40], which might be attributed to differences in etiological factors and/or patient populations.

Cytokines also regulate the transcription of guanosine triphosphate cyclohydrolase (GTPCH) and induce the expression of GTPCH genes in T-lymphocytes, macrophages and various other cells. As a consequence of immune stimulation, activated macrophages excrete neopterin, which can be found in plasma, urine and cerebrospinal fluid [41,42]. These processes are shown in Figure 1. In physiological conditions neopterin causes vasodilatation. However, after excessive immune stimulation the elevated neopterin levels can lead to vasoplegia, oxidative stress, and peroxynitrite-related cytotoxicity, contributing to cell damage [43]. Thus, neopterin is regarded as a marker of cellular immune activation and oxidative stress, its plasma levels reflecting the amount of immune activation and oxidative stress [44].

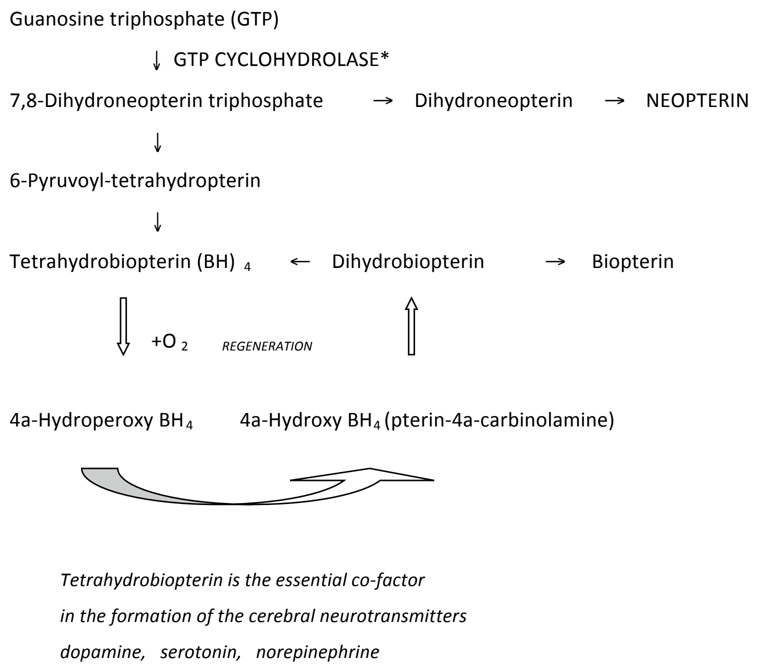

Figure 1. Biosynthesis of neopterin and tetrahydrobiopterin.
*Increased enzyme activity due to immune activation results in an increased neopterin level.

Oxidative stress hypothesis

Brain tissue is vulnerable for damage due to hypoxia and oxidative stress because of its dependence on aerobic metabolism, high mitochondrial oxidative metabolism, low antioxidant capacity and high lipid content [45]. Besides the plasma neopterin level, other measures of oxidative stress are the plasma levels of the amino acid citrulline and the citrulline/arginine ratio. These amino acids are involved in the formation of nitric oxide, an oxygen radical (ROS), in a reaction using tetrahydrobiopterin as essential co-factor (Figure 2) [46,47]. In physiological conditions, nitric oxide enhances vascular dilatation and may stabilise cell membranes. However, in conditions of oxidative stress, nitric oxide is associated with oxidative damage and cellular death [48]. Especially in combination with reduced levels of tetrahydrobiopterin nitric oxide toxicity is enhanced, leading to brain tissue damage, as found in Alzheimer dementia and other degenerative brain diseases [41,49].

BH_4

Essential Co-factor

Phenylalanine ➔ Tyrosine

Norepinephrine ↑

Tyrosine ➔ L-DOPA → Dopamine → HVA

Tryptophan ➔ 5-Hydroxytryptophan → Serotonin (5-HT) → 5-HIAA

Arginine ➔ Citrulline + NO

Figure 2. Biosynthesis of cerebral neurotransmitters and nitric oxide.

→ Biochemical reactions in which tetrahydrobiopterin (BH_4) is an essential co-factor.
BH_4:Tetrahydrobiopterin, 5-HIAA: 5-Hydroxyindoleacetic acid, 5-HT: 5-Hydroxytryptamine or Serotonin, HVA: Homovanillic acid, L-DOPA: 3,4-Dihydroxy-L-phenylalanine, NO: Nitric Oxide.

Monoamine hypothesis

Disturbances of several cerebral neurotransmitters are associated with the development of delirium. Amino acids play an important role in the synthesis of neurotransmitters. In the formation of serotonin, norepinephrine and dopamine (as well as the conversion of phenylalanine into tyrosine), tetrahydrobiopterin is an essential co-factor [41]. The preoperative plasma concentration of tryptophan (the precursor of serotonin) and the ratio of tryptophan to the other large neutral amino acids (LNAAs) were shown to be diminished in patients undergoing cardiac surgery [50]. However, a decreased plasma tryptophan ratio as a predictor for delirium could not be found in a replication study [51], although the ratio of phenylalanine to the other LNAAs was increased postoperatively in delirious patients when compared to non-delirious patients [51]. Because phenylalanine is the precursor of dopamine or norepinephrine, this points towards an increased biosynthesis of these neurotransmitters. The plasma level of phenylalanine also influences the cerebral tryptophan availability, because both amino acids enter the brain by means of the same LNAA-transporter protein, for which phenylalanine has a higher affinity [52], thus lowering the brain levels of the serotonin precursor, tryptophan. These findings suggest a decreased serotonergic and an increased dopaminergic and norepinephrinergic neurotransmission in delirium. Figure 2 shows the relevant pathways. Clarification of the described pathophysiological pathways in delirium might lead to the development of alternative or more effective treatments for delirium.

Cognitive functioning after delirium

In general, delirium is perceived as a grave but transient condition, in which the prognosis is determined mainly by the patient's physical illness, age, and overall physical condition [1]. In 1990 Lipowski stated in his monograph about delirium: 'The most common outcome of delirium is full recovery' [1]. This statement, however, is called into question, with increasing numbers of studies emphasizing the association of delirium with various serious adverse outcomes, such as increased medical complications, increased length of hospital or intensive care stay, increased institutionalisation, decreased cognitive functioning, decreased quality of life, and increased mortality [53-56]. It has been subject of dispute whether the reported decrease in cognitive functioning is pre-existing or caused by delirium itself or whether it is a reflection of the somatic diseases underlying delirium.
Studies that measured cognitive functioning before and after delirium often used the Mini Mental State Examination [57], in which different cognitive domains are grouped together and to date specific cognitive domains were not assessed in relation to delirium. One study examined specific cognitive domains in cancer patients with delirium, but in this case delirium was not measured daily [58]. Assessing specific domains of cognitive functioning that are associated with delirium is relevant, because especially executive functioning is associated with negative consequences in daily functioning as perceived by the patient and caregivers [59,60]. Furthermore, it could provide insight into the question whether delirium and different types of dementia share similar pathophysiological mechanisms. At present, studies assessing different domains of cognitive functioning, before and after delirium, and using validated tests are lacking.

Aims and outline of the thesis

In the Erasmus MC, University Medical Center Rotterdam (the Netherlands), approximately 40% of all psychiatric consultations are carried out in patients with delirium. Because of proportional ageing of the general population and increasing complexity of medical interventions, a rise of the incidence of delirium can be expected. Despite the large impact of delirium on the patients and their caregivers, little research is performed in this field. In a collaboration of the Departments of Cardiothoracic Surgery and Psychiatry of the Erasmus MC, research was conducted concerning pathogenetic and clinical predictors of delirium and cognitive functioning after delirium in older patients undergoing cardiac surgery. This thesis describes the first results of this research program.

Especially older patients are at risk of a delirium after cardiac surgery, but few studies on preoperative and operative predictors of delirium were executed in older patients. Therefore, preoperative and operative predictors of delirium were examined in a group of patients aged 70 or older, scheduled for elective cardiac surgery (Chapter 2).

As a first step in the process of finding an objective quantitative method to assess rest-activity patterns in delirium, the use of wrist-actigraphy after cardiac surgery was explored in patients without a clinically relevant delirium, in patients with a short delirium (2-3 days) and in patients with a sustained delirium (4 days or more, Chapter 3). In addition, the use of wrist-actigraphy for early recognition of delirium was explored in older patients after cardiac surgery (Chapter 4).

Previous studies in patients with delirium after cardiac surgery showed that delirium was associated with decreased plasma tryptophan and increased phenylalanine levels [50,61]. In order to replicate these findings and based on hypotheses involving immune activation, oxidative stress and amino acid related changes in cerebral neurotransmission in delirium, the association between pterins and amino acids and delirium was investigated (Chapter 5).

Furthermore, delirium has been associated with diminished cognitive functioning. It was unclear whether cognitive dysfunction is pre-existing, or caused by delirium itself, or by somatic diseases underlying delirium. In a prospective cohort study, the association between delirium and different cognitive domains before and long-term after cardiac surgery was investigated using validated neuropsychological tests (Chapter 6).

In a general discussion the findings of the previous chapters are reviewed and discussed (Chapter 7), followed by a summary (Chapter 8). Finally, the summary is also presented in a Dutch translation (Chapter 9).

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Chapter

2

Preoperative and operative predictors of delirium after cardiac surgery in elderly patients

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2

ABSTRACT

Objectives Delirium is a common complication in elderly patients after cardiac surgery and is associated with adverse outcomes including prolonged hospital stay and increased mortality. Therefore, prevention or early detection of delirium is indicated. Our objective was to identify preoperative and operative characteristics that could predict delirium after cardiac surgery in elderly patients.

Methods We conducted a prospective cohort study in which we analysed 201 patients of 70 years and older who underwent cardiac surgery, for developing a delirium. Patients were assessed daily using the Confusion Assessment Method-Intensive Care Unit (CAM-ICU).

Results Sixty-three patients (31%) developed a delirium after cardiac surgery. The Mini-Mental State Examination (MMSE) score prior to surgery was lower in the delirious patients as compared to the non-delirious patients (27 vs. 28, $P = 0.026$), creatinine level was higher (98 vs. 88 µmol/l, $P = 0.003$), and extracorporeal circulation (ECC) time was longer (145 vs. 113 min, $P < 0.001$). Mortality during the first 30 days after surgery in patients with a delirium was significantly higher than in the non-delirious patients (14% vs. 0%, $P < 0.001$).

Conclusions Low MMSE score and high creatinine level prior to surgery, as well as increased ECC time are important independent predictors of delirium. In addition, delirium is an important predictor of 30-day mortality. Patients with a substantial risk for delirium should be candidates for interventions to reduce postoperative delirium and potentially improve overall surgical outcomes.

Keywords: Predictors, Delirium, Postcardiotomy, Cardiac surgery.

INTRODUCTION

Delirium is a common complication in elderly patients after cardiac surgery. Estimations of the prevalence of a delirium after cardiac surgery varies between 2% and 73% [1]. In patients above 60 years, the prevalence has been reported to be in the range of 30% to 52% [2,3]. Increasing numbers of elderly patients are treated with cardio-thoracic surgery, due to advances in surgical and anaesthetic techniques. With an ageing of the population benefitting from these medical advances, delirium is a growing problem after cardiac surgery. Systematic screening for the presence of a delirium in populations at risk is needed to avoid inadequate detection and, as a consequence, inadequate treatment.

Hallmark symptoms of a delirium are consciousness disturbances, concentration disorders and cognitive disorders, such as disorientation, memory disturbances and hallucinations. The motoric presentation of a delirium may vary from an apathetic, inactive state to an agitated, hyperactive state. The variability of presentation, abrupt onset and fluctuating course can make recognition of a delirium difficult. According to patients, delirium and subsequent cognitive decline are among the most feared adverse events following surgery [4]. In epidemiological data, delirium is associated with increased morbidity, prolonged hospital stay, diminished functional outcome and increased mortality [5]. Preventive interventions addressing geriatric and nursing care have shown to decrease the incidence of delirium [6] and prophylactic use of haloperidol diminished delirium severity and duration [7].

Well-established risk factors for delirium are age and medical co-morbidity. In addition, cardio-thoracic operative risk factors, which are included in the EuroSCORE (European System for Cardiac Operative Risk Evaluation), are associated with both mortality and delirium after cardiac surgery [2,8,9]. Furthermore, we assume that increased duration of surgery increases the risk for delirium, as it is an indicator of the complexity of the procedure and severity of the cardiac disease [10,11]. The duration of surgery is also associated with an increase of embolic load to the brain after extra corporeal circulation [12] and increased chemokine release [13].

Despite the impact and increasing interest of delirium after cardiac surgery and the aging population, few prospectively studies have been done regarding the risk factors of a delirium in specifically elderly patients. Therefore, the objective of this study is to identify preoperative and operative characteristics that enable us to predict delirium after cardiac surgery in elderly patients.

MATERIALS AND METHODS

Subjects

Between April 2005 and April 2008, all patients aged 70 years and older, who were scheduled to undergo cardiac surgery at the Department of Cardiothoracic Surgery of the Erasmus MC, were eligible to participate in our prospective cohort study. The patients were invited to

participate in the study after having received detailed information in both oral and written form.
Exclusion criteria were surgery in which 'deep hypothermia', circulatory arrest or an emergency procedure was required and patients with signs of a pre-existing delirium or who were not able to speak sufficient Dutch or refused to provide written informed consent. The study protocol was approved by the Medical Ethical Committee of the Erasmus MC and conducted in accordance with the criteria of Good Clinical Practice (Declaration of Helsinki, 2004) and Dutch legal regulations for studies in humans.

Procedure

Before surgery, demographic and medical characteristics, such as the medical history, were recorded. The Charlson comorbidity index (CCI) and the EuroSCORE were used to measure medical co-morbidity and specific cardio-surgical risk factors and operative mortality risk, respectively [14,15]. General cognitive functioning was measured using the Mini-Mental State Examination (MMSE) [16]. The presence of a pre-existing delirium was assessed using the Confusion Assessment Method-Intensive Care Unit (CAM-ICU) [17], which applies the definition of delirium in the Diagnostic and Statistical Manual of mental disorders fourth edition, (DSM-IV) [17]. Delirium is defined as a neuropsychiatric disorder of acute onset, with disturbances of consciousness, attention, cognition and/or perception, not better accounted for by a pre-existing, established or evolving dementia, which tends to fluctuate during the course of the day. In addition, venous blood samples were obtained for routine pre-operative screening and research-specific measurements. All relevant metabolic and electrolyte disturbances were corrected prior to the surgical procedures.
On the night before surgery, all patients were prescribed temazepam (10-20 mg) followed by lorazepam (1 mg) just before the surgical procedure. Standardized anaesthetic management was used in all patients as described previously [18]. In short: Anaesthesia was induced by midazolam (0.1 mg/kg) and sufentanil (2 µg/kg). Muscle relaxation was induced with pancuronium (0.1-0.2 mg/kg) and was not reversed. After intubation and the start of ventilation, a central venous line was inserted through the right internal jugular vein. Anaesthesia was maintained with propofol (2-4 mg/kg/hr) and sufentanil (1 µg/kg) as needed. Antibiotic prophylaxis was given with cefazoline for 24 h. None of the patients received corticosteroids. During the surgical procedure, operative characteristics were recorded including the type of surgical procedure [e.g. coronary artery bypass grafting (CABG), valve surgery or both], the duration of the surgical procedure, the ECC time and the aorta cross clamp (AoX) time.
Postoperatively, pain medication consisted of intravenous morphine (starting dose 0.0125 mg/kg/hr). The patients were assessed daily, between 10.00 and 12.00 h, in order to prevent possible bias due to circadian rhythms or care programmes. The assessments were

done, by a senior psychiatrist and/or trained researchers. In these assessments, the medical and nursing records of the preceding 24 h were evaluated. The presence of a delirium was diagnosed using the CAM-ICU. We predefined that a delirium lasting more than 1 day, as assessed using the CAM-ICU, would be considered clinically relevant. The first day after surgery was not taken into account because of possible protruded effects of the anaesthetic procedure. Whenever a patient developed a delirium, standardized psychiatric treatment according to APA guidelines was applied [19]. In delirious patients haloperidol was titrated to the lowest effective dose and benzodiazepine use was diminished or stopped. In case of severe insomnia mianserin (10-30 mg) was added ante noctem. In case of insomnia in non-delirious patients temazepam (10-20 mg) was used.

Furthermore, medical characteristics (e.g. the use of intravenous lines, catheters) and adverse events (e.g. re-thoracotomy, deep sternal wound infection, renal failure and respiratory failure) were recorded.

The patients were assessed daily until discharge from the hospital or for a maximum of 7 days following surgery. Because the majority of the patients are discharged from the hospital within 5 or 6 days after surgery, only a few patients stayed in the hospital longer than 7 days. Finally, the 30-day mortality was recorded using data from the Dutch municipal administration.

Questionnaires and biochemical measurements

The CCI was used to assess the burden of medical co-morbidity [14]. The scale was designed to classify prognostic co-morbidity in longitudinal studies. It assesses the presence of factors associated with an increased mortality risk. The mortality rates in the original data set ranged between 12 and 85%, depending on the co-morbidity index scores.

The MMSE is a frequently used clinical tool to asses global cognitive functioning in hospital patients [16]. It consists of 11 questions and requires 5 - 10 min to administer. Although the test characteristics of the MMSE have been criticized (sensitivity 66 - 89% and specificity 78 - 99%), in a clinical context it proves to be a feasible tool to measure cognitive functioning, even in relatively ill patients.

The CAM-ICU [20] is a delirium detection instrument, based on the criteria for delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [17]. The CAM-ICU contains four items and can be administered in < 5 min by trained interviewers who can be non-clinicians. A positive diagnosis requires the presence of an acute onset or fluctuating course of mental status as well as inattention and either disorganized thinking or altered level of consciousness. The sensitivity and specificity are reported to range between 92-100% and 83-100%, respectively, depending on the reference population.

The Hospital Anxiety and Depression Scale was used to measure pre-operative anxiety and depression in our patients [21].

Using routine analytic techniques, the venous blood samples were prepared to measure the blood assays. These consisted of several routine laboratory measurements, including C-reactive protein and plasma creatinine levels.

Statistical methods

Differences between the demographic and surgical characteristics of the delirious and non-delirious patients were evaluated using the χ^2 test for categorical data and Student *t*-test for continuous data, if normally distributed. The Mann-Whitney *U*-test was used if continuous data were skewed (Kolmogorov-Smirnov test).

Univariate logistic regression techniques were used to calculate unadjusted (crude) odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All predictors were tested for a linear relationship with the presence of a delirium after cardiac surgery. In the case of a non-linearity, dichotomisation was performed using the mean or median value of the non-delirious patient group for the cut-off value. Sensitivity analyses were used to explore the effect of alternative dichotomisations. Possible predictors of delirium were analysed by multivariable forward stepwise likelihood ratio logistic regression with 0.25 and 0.025 alpha levels for entry and removal, respectively. All significant main factors were checked for collinearity and interaction effects. Model selection was based on likelihood ratio test statistics. The goodness of fit was assessed with the Nagelkerke R^2 and the Hosmer and Lemeshow test. The model's ability to discriminate between patients with and without postoperative delirium was estimated by the area under the receiver-operating characteristic (ROC) curve. All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA, version 17.0).

RESULTS

In the inclusion period, 369 patients were eligible and invited to participate in the study. Two hundred eleven patients provided their informed consent to participate in the study. Ten patients withdrew their informed consent before the first measurement or could not comply with the protocol. Our final analyses were based on 201 subjects.

Ninety-four patients did not score positive on the CAM-ICU during the follow-up whereas 44 patients were CAM-ICU-positive on day 1 after surgery. According to our definition these patients were grouped in the non-delirious group. A clinically relevant delirium occurred in 63 (31%) of the 201 patients of 70 year and older who underwent cardiac surgery. The mean delirium duration was 3.3 days. Forty-five patients (71%) of the delirious patients showed a continuous delirium starting after surgery, and 18 patients (29%) showed a fluctuating course of the delirium, with one or more non-delirious days within the study period. The mean age of the patients was 76.1 years, and no significant differences in age or gender between the delirious and non-delirious groups were found (76.7 vs. 75.9 years and 59 vs. 61% males, respectively; Table 1).

Table 1. Patient demographics and medical characteristics of non-delirious and delirious patients

	Non-delirious n=138	Delirious n=63	P-value
Gender males n (%)	84 (61)	37 (59)	0.774
Age in years mean (SD)	75.9 (3.7)	76.7 (3.9)	0.136
Marital status n (%)	101 (73)	43 (68)	0.472
Ethnicity n (%)	136 (99)	60 (95)	0.186
BMI mean (SD)	26.5 (3.2)	26.6 (4.2)	0.867
Hypertension n (%)	70 (51)	27 (43)	0.300
Diabetes without complications n (%)	34 (25)	12 (19)	0.417
Diabetes with complications n (%)	4 (3)	3 (5)	0.569
Hyperlipidaemia n (%)	41 (30)	16 (25)	0.530
Creatinine µmol/l median (IQR)	88 (25)	98 (42)	**0.003**
Previous cardiac surgery n (%)	7 (5)	10 (16)	**0.014**
Left ventricle function			0.982
Moderate n (%)	12 (9)	6 (10)	
Poor n (%)	2 (1)	1 (2)	
Myocardial infarction n (%)	29 (21)	18 (29)	0.246
Extracardiac arteriopathy n (%)	12 (9)	8 (13)	0.388
Cerebrovascular disease n (%)	19 (14)	13 (21)	0.208
Pre-hospitalisation n (%)	22 (16)	12(19)	0.482
MMSE score median (IQR)	28 (3)	27 (4)	**0.026**
HADS anxiety subscale Mean (SD)	6.9 (2.8)	7.0 (2.3)	0.770
HADS depression subscale Mean (SD)	4.3 (3.2)	4.6 (3.2)	0.534
CCI median (IQR)	1 (1)	2 (1)	**0.013**
CCI age median (IQR)	4 (1)	5 (2)	**0.005**
Logistic EuroSCORE median (IQR)	5.0 (4.0)	7.0 (5.7)	**<0.001**
Isolated CABG or valve n (%)	100 (72)	36 (57)	0.058
Valve + coronary n (%)	26 (19)	15 (24)	0.212
Double valve + coronary n (%)	12 (9)	12 (33)	**0.024**
AOX time median (IQR)	74 (47)	94 (67)	**0.001**
ECC time median (IQR)	113 (59)	145 (69)	**<0.001**

AOX time: Aorta Cross clamp time, CABG: Coronary Artery Bypass Graft, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, CCI age: Charlson Comorbidity Index with age, ECC time: Extra Corporeal Circulation time, Ethnicity: Caucasian compared to other, Extracardiac arteriopathy as described in EuroSCORE, HADS: Hospital Anxiety and Depression scale, IQR: Inter Quartile Range, Marital status: married vs. widow, single or divorced, MMSE: Mini-Mental State Examination, SD: Standard Deviation.

2

The preoperative MMSE score was significantly lower in the delirious patients as compared to the non-delirious patients (27 vs. 28, $P = 0.026$). In addition, the preoperative creatinine level was significantly higher in the delirious group compared to the non-delirious group (98 vs. 88 µmol/l, $P = 0.003$).

The CCI was significantly higher in delirious patients as compared to non-delirious patients (2 vs. 1, $P = 0.013$; Table 1). When the Charlson comorbidity score was corrected for age (CCI age), the delirious group still showed significantly higher scores as compared to the non-delirious group (CCI age: 5 vs. 4, $P = 0.005$). Delirious patients also showed significantly increased EuroSCORE levels as compared to non-delirious patients (logistic EuroSCORE: 7.0 vs. 5.0, $P < 0.001$; Table 1). In univariate logistic regression analyses, congestive heart failure, previous cardiac surgery, low MMSE score and high creatinine level prior to surgery, and increased duration of surgery were associated with an increased risk for the development of a delirium after cardiac surgery.
The most frequently performed surgical procedure was CABG, which was performed in 130 (64.7%) patients. All procedures were on-pump except for one. In total 71 aortic valves, 54 mitral valves and 19 tricuspid valves were repaired or replaced (Table 2). None of the patients underwent a Bentall-type operation. The percentage of delirium increased from 26% to 50% as the surgical procedure became more complex. The ECC time (145 min vs. 113 min, $P < 0.001$) and AoX-time (94 vs. 74 min, $P = 0.001$) were significantly longer in the delirious group when compared to the non-delirious group (Table 1).

Table 2. Surgical procedure in non-delirious and delirious patients

	Non-delirious n=138	**Delirious n=63**	**P-value**
CABG n (%)	60 (43)	23 (37)	0.352
AVR n (%)	25 (18)	6 (10)[1]	0.124
AVR + CABG n (%)	23 (17)	8 (13)	0.471
MVP n (%)	21 (15)[2]	14 (22)[3]	0.227
MVP + CABG n (%)	3 (2)[4]	7 (11)[5]	0.006
MVP + AVR (+ CABG) n (%)	6 (4)[6]	5 (8)[7]	0.378

AVR: Aortic Valve Replacement, CABG: Coronary Artery Bypass Graft, MVP: Mitral Valve Annuloplasty, Mitral Valve Replacement, TVP: Tricuspid Valve Annuloplasty, TVR: Tricuspid Valve Replacement.
[1]including 1 TVP, [2]including 7 TVP and 3 MVR, [3]including 7 TVP and 3 MVR, [4]including 1 MVR, [5]including 2 MVR, [6]including 1 TVP, 1 TVR and 2 MVR+ 2 CABG, [7]including 1 TVP, 1 TVR and 1 MVR+ 4 CABG.

Except for atrial fibrillation or flutter, which was equally divided between the delirious and non-delirious group [respectively, 33 patients (52%) vs. 72 patients (52%), $P = 0.100$], a higher percentage of patients in the delirious group experienced one or more complications as compared to the non-delirious group (Table 3).

Mechanical ventilation (>1 day) occurred more frequently in the delirious group compared with the non-delirious group (21 vs. 1%, $P < 0.001$). After surgery, circulatory support [Intra-aortic balloon pump (IABP)] was used in two patients, who were in the delirious group (3 vs. 0%). Also, other adverse events were increased in delirious patients as compared to non-delirious patients (e.g. re-thoracotomy for persistent blood loss: 17 vs. 7%, $P = 0.021$, renal failure: 14 vs. 0%, respiratory failure: 8 vs. 0%, deep sternal wound infection 5 vs. 1% and re-operation due to graft or valve dysfunction 2 vs. 1%, respectively). Three patients in the delirious group experienced symptoms, which could have been caused by a transient ischaemic attact (< 24h neurological deficit) or stroke. In these cases a computed tomography scan was performed, which didn't show (new) signs of cerebral ischemia.

Table 3. Complications and 30-day mortality of non-delirious and delirious patients

	Non-delirious n=138	**Delirious n=63**	**P-value**	**Odds Ratio (95%CI)**
Atrial fibrillation or flutter n (%)	72 (52)	33 (52)	0.100	1.63 (0.91-2.91)
Mechanical ventilation (>1 day) n (%)	1 (1)	13 (21)	**<0.001**	12.20 (1.55- 95.99)
Circulatory support (IABP) n (%)	0 (0)	2 (3)	(1	
Re-thoracotomy n (%)	9 (7)	11 (17)	**0.021**	3.01 (1.18-7.69)
Re-operation n (%)	2 (1)	1 (2)	0.945 (1	
Deep sternal wound infection n (%)	1 (1)	3 (5)	0.100 (1	
Renal failure n (%)	0 (0)	9 (14)	(1	
Respiratory failure n (%)	0 (0)	5 (8)	(1	
Length of ICU stay median (IQR)	1(0)	2(4)	**<0.001**	1,21 (1,11-1,31)
Length of hospitalization median (IQR)	6(3)	9(8)	**<0.001**	2.12 (1,57-2,88)
Early mortality (< 30 days) n (%)	0 (0)	9 (14)	(1 (2	

IABP: Intra Aortic Balloon Pump, ICU: Intensive Care Unit, IQR: Inter Quartile Range, Re-thoracotomy: for persistent blood loss, re-operation: dysfunction of graft or valve, renal failure: need of dialysis, respiratory failure: need of re-intubation.
(1 Statistical testing hampered or impossible due to low or zero values
(2 causes of death: pneumonia (n=3), mesenteric ischemia (n=2), sudden cardiac death (n=1), heart failure (n=1), heart failure in combination with sepsis (n=1), and unknown (n=1).

In addition, the 30-day mortality was significantly increased in the delirious group with nine patients (14%), compared to none (0%) in the non-delirious group. The causes of early death (<30 days) were: three cases of pneumonia, two of mesenteric ischaemia, one sudden cardiac death, one heart failure, one heart failure in combination with sepsis and of one patient the death cause remained unknown. Another three patients died later during their hospital stay due to heart failure (n=2, respectively, 33 and 53 days after surgery) and respiratory insufficiency (n=1, 118 days after surgery). All of the patients that died within 30 days after surgery or later during the hospitalisation showed a clinically relevant delirium.
In a multiple logistic regression analysis, three independent risk factors of postoperative

delirium were identified (Table 4), i.e. preoperative MMSE score (adjusted OR 2.32; 95% CI 1.20-4.46), creatinine level (adjusted OR 1.02; 95% CI 1.00-1.03) and ECC time (adjusted OR 1.01; 95% CI 1.01-1.02). The 'goodness of fit' of this model was assessed with Nagelkerke R^2 (0.184) and the Hosmer and Lemeshow test (χ^2=11.425, df=8, P = 0.179). The model's ability to discriminate between patients with and without postoperative delirium, estimated by the area under the ROC curve, was 0.71 (95% CI 0.63-0.79, P < 0.001).

Table 4. Multiple logistic regression model of the predictors of delirium after cardiac surgery

	OR (CI)	**P-value**
MMSE score ≤ 27	2.32 (1.20-4.46)	0.012
Creatinine µmol/l	1.02 (1.00-1.03)	0.015
ECC time per min	1.01 (1.01-1.02)	<0.001
Constant	0.01	

Nagelkerke R^2 (0.184), Hosmer and Lemeshow test (χ^2=11.425, df=8, p=0.179), (ROC) curve, 0.712 (95% CI: 0.634-0.789, p<0.001).
ECC time: Extra Corporeal Circulation time, MMSE: Mini-Mental State Examination.

DISCUSSION

Patients, who developed a delirium after cardiac surgery, showed a lower cognitive functioning before surgery as measured with the MMSE, increased co-morbidity and increased EuroSCORE when compared with patients who did not become delirious. The surgical procedures were more complex, in delirious patients when compared with non-delirious patients, and the duration of ECC and AoX time were longer. After surgery the delirious group experienced more adverse events, and these adverse events could have contributed to the causative factors of a delirium. Moreover, the delirious patients showed an increased 30-day mortality rate.

A delirium incidence of 31 % was found in patients of 70 years and older. This incidence is in the low range as compared to other studies with elderly populations [3,22].

Age is a well-established predictor for the occurrence of a delirium [2,8,9]. In our study, the delirious group was on average 0.8 years older than the non-delirious group. This difference was, however, not significant and might be explained by the relative small age range of participants in this study (e.g. 70-85 years).

Although it is not certain why elderly patients, in particular, are at risk for the development of delirium, there are several hypotheses. For example, age is associated with increased atherosclerosis and endothelial dysfunction [22]. As a consequence elderly patients have an increased risk of cerebral embolization. Furthermore, cerebral atherosclerosis combined with postsurgical inflammatory changes may inhibit cerebral blood flow [13]. There are also neurochemical factors predisposing elderly patients for a delirium, such as lack of cholinergic reserves [13]. This risk will be provoked by commonly used medications with anticholinergic activity such as ipratropium and opiate analgesics.

In our study with elderly patients we found three independent predictors of postoperative delirium after cardiac surgery: reduced preoperative MMSE score, increased creatinine level and increased ECC time.

The presence of creatinine level in our multivariate model suggests that renal dysfunction is an important factor. Renal dysfunction has been identified as important risk factor of mortality after cardiac surgery [15,23] and has been described previously as predictor of delirium [2]. It frequently reflects poorly controlled hypertension and diabetes or, in general, more severe and extensive vascular disease. Early attention to correct renal function may help prevent development, persistence or severity of delirium.

Prior decreased cognitive function (low MMSE score) is an expected risk factor for developing cognitive problems postoperatively, as well as later in life [5,22]. However, milder degrees of cognitive impairment than the traditional threshold of an MMSE score of ≤23, also increases the risk of delirium substantially. According to our data, even elderly patients with a MMSE score of 27 or lower show an increased risk for delirium, suggesting a possible indication for prophylactic haloperidol (1-2 mg) use.

Increased duration of surgery has previously also been described as a predictor of delirium after cardiac surgery [10,11]. This might be caused by increased chemokine release by longer duration of surgery [22]. Furthermore, the duration of the surgical procedures is a good indicator of complexity of the procedure. Longer duration of surgery and ECC time may increase the embolic load to the brain [12].

In recently published studies, a positive correlation between EuroSCORE and postoperative delirium was found [9]. We can confirm this relationship in our study with only elderly patients. The fact that the EuroSCORE contains important risk factors for postoperative mortality explains the positive correlation.

Moreover, we confirm the known increased risk of early mortality after surgery in patients with a delirium [1,5]. This emphasizes the importance of predicting and possible preventing of a delirium.

A limitation of the study is that it was conducted in a specific group of elderly patients undergoing cardiac surgery. This warrants carefulness in extrapolating the findings to other patient populations. Another limitation is that the patients' recollection of their own medical history was used to establish earlier diagnoses. All medical records were reviewed to minimize discrepancies due to forgetting or misunderstanding of medical facts for each subject. This has, however, no impact on the final model because MMSE score, creatinine level and ECC time were measured in our institution. Finally, a limitation is that we did not have a validation sample.

Despite these limitations, the strengths of this study are the prospective design and the relative large population of elderly patients participating in this study. In addition, the use of valid and reliable instruments (e.g. CAM-ICU) to identify patients with DSM-IV-defined delirium by experienced and trained researchers or a senior psychiatrist. Daily assessments until discharge from the hospital or until 7 days after surgery provided a detailed longitudinal follow-up of the delirious symptoms over time. Any fluctuation of delirium symptoms was recorded, ensuring the validity of the findings. Furthermore, the cardiac surgical procedures in our study consisted not only of CABG, but also valve surgery or both. To our knowledge, this is the first prospective study clarifying the prevalence and risk factors of a delirium after cardiac surgery, specifically in elderly patients.

In conclusion, the prevalence of delirium after cardiac surgery in elderly patients is high. The three identified predictors (reduced preoperative MMSE, increased creatinine level and increased ECC time) can easily be measured and, therefore, can be used to identify patients at increased risk for postoperative delirium after cardiac surgery. In these high risk elderly patients, preventive interventions can be taken such as geriatric assessments before surgery and usage of multi-component prophylactic measures [6].

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Chapter

3

Disturbed circadian motor activity patterns in postcardiotomy delirium

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ABSTRACT

Aims More than 20% of elderly patients of 65 years or older may develop a delirium after cardiac surgery. Patients with delirium frequently show a disturbed 24-hr motor activity pattern, but objective and quantitative data are scarce. Our aim was to quantify motor activity patterns in elderly patients with or without a postcardiotomy delirium after elective cardiac surgery.

Methods Wrist-actigraphy was used to quantify 24-hr motor activity patterns for a 5-day period following cardiac surgery in 79 patients of 65 years or older. Clinical state was monitored daily by means of the Confusion Assessment Method-Intensive Care Unit and the Delirium Rating Scale-Revised 98.

Results The activity Amplitude, and the daytime Activity/minute and Restlessness index were significantly higher and daytime number of Immobility minutes significantly lower for the patients without delirium or with short delirium episodes, as compared to patients with a sustained delirium (>3 days).

Conclusions Actigraphy proves to be a valuable instrument for evaluating motor activity patterns in relation to clinical state in patients with a postcardiotomy delirium.

Keywords: actigraphy, cardiac surgery, motor activity, postcardiotomy delirium.

INTRODUCTION

A delirium is a frequently occurring organic psychiatric syndrome of acute onset that can be characterized by cognitive dysfunction, attentional abnormality, increased or decreased psychomotor activity, and a disturbed sleep-wake cycle.[1,2] The incidence of a delirium in patients of 65 years or older in the general hospital varies between 5 and 31%, with an average of about 18%.[3] After cardiac surgery this percentage is higher: about 23% of patients of 65 years or older may develop a delirium.[4] The presence of a delirium is associated with longer hospital stay and increased risk of mortality.[5,6]

Patients with a delirium frequently show a disturbed 24-hr motor activity pattern, with increased motor activity during the night. At the clinical level, a distinction can be made between hyperactive, hypoactive or mixed subtypes of delirium,[7,8] with presumed differences in underlying pathophysiology and responsivity to therapeutic interventions.[8] The hypoactive subtype of delirium is less well recognised.[9,10] At present, data regarding motor restlessness, disturbed rest-activity patterns, and delirium subtypes are based on assessments by means of validated rating scales such as the Delirium Rating Scale-Revised-98 (DRS-R98),[11] or on medical file reports of clinicians or nurses regarding incidences of extreme restlessness of the patient. However, objective and quantitative data of recovery of 24-hr motor activity patterns of patients following elective cardiac surgery are scarce, let alone of patients who develop a postcardiotomy delirium.

Wrist-actigraphy can be used as an objective method to assess 24-hr patterns of spontaneous motor activity for prolonged periods of time in various environments. The method accurately distinguishes rest from activity periods in a valid and reliable way.[12,13] In a variety of psychiatric (e.g. major depression) and neurological (e.g. Alzheimer's disease) patient categories, wrist-actigraphy has been used to quantify disturbances in sleep-wake schedule, alterations in diurnal rest-activity patterns, as well as psychomotor disturbances (psychomotor retardation or agitation).[14-17] In relation to this study, it is relevant to mention that the method also proved to be feasible for studying sleep-wake activity patterns in demented nursing home patients,[18] in demented patients with a delirium,[19] and following anesthesia as an objective indication of change in the depth of the anesthetics and sedation and its associated events during surgery and recovery.[20]

Considering the clinical importance of disturbed motor activity patterns in postcardiotomy delirium, clarification of its role has relevance for diagnostic purposes, for early recognition of subtypes of delirium that may improve prognosis by early treatment, and for the development of effective treatment strategies. Therefore, we performed an observational study to explore the usefulness of wrist-actigraphy to quantify characteristics of 24-hr motor activity patterns during a 5-day postoperative period after elective cardiac surgery in patients who did or did not develop a postcardiotomy delirium. As a first approach, we focused on the duration of the delirium in relation to recovery of circadian rest-activity patterns.

METHODS

Subjects

Eighty-eight patients of 65 years and older who underwent elective cardiac surgery at the department of Cardiothoracic Surgery of the Erasmus Medical Center in Rotterdam were included in the study. Specific exclusion criteria were: patients who experienced a 'deep cooling' or 'circulator arrest' as a requirement for surgery and emergency surgery, no sufficient understanding of the Dutch language, pre-operative dementia or delirium (clinical assessment), and not enough compliance to follow the protocol. In addition, subjects were excluded if they developed a delirium during the course of the post-operative week (n=3), or were comatose (n=6), leaving 79 patients for the present analyses. All patients provided written informed consent before entering the study. The diagnosis delirium was assessed and evaluated daily by a senior psychiatrist and/or trained researchers based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[21] and the four-item diagnostic Confusion Assessment Method-Intensive Care Unit (CAM-ICU)[22] algorithm.[23]
Only a post-operative delirium lasting more than one day was judged to be clinically relevant, because of the frequently occurring protracted effects of narcotics or sedating drugs in elderly patients. The patients were divided into three groups: (i) a group with non-clinically relevant delirium, consisting of patients who did not develop a delirium or were delirious only during the first post-operative day ('Non-cr-Del'; n=46; 26 men; mean age=72.9 years, SD=4.9); (ii) a group with a post-operative delirium of short duration, consisting of patients who were delirious for 2 or 3 days directly following surgery ('Short-Del'; n=16; 9 men; mean age=75.2 years, SD=4.1); and (iii) a group with a sustained post-operative delirium, consisting of patients who were delirious for 4 days or more directly following surgery ('Sustained-Del'; n=17; 9 men; mean age=75.2 years, SD=4.5).
The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Center and conducted in accordance with the criteria of Good Clinical Practice (Declaration of Helsinki, 2004).

Procedure

The patients underwent elective cardiac surgery (coronary artery bypass graft, valve surgery, or both) at the department Cardiothoracic Surgery of the Erasmus Medical Center in Rotterdam. Eligible patients were invited to participate in the study after having received detailed information in both oral and written form. All patients provided written informed consent. Surgery was scheduled at variable times during the day; however, most patients were operated during the morning. As soon as the patients returned from surgery to the intensive care unit (usually in the afternoon; day 0), the actigraph was placed on the non-dominant wrist for continuous measurement of 24-hr motor activity patterns during a period of 6 days. On day 6 after surgery the actigraph was removed, or sooner when the patients were transported to another hospital. Daily, between 9.00 hours and 12.00 hours, the CAM-ICU was assessed by a senior psychiatrist or trained researcher. In the case of a positive CAM-ICU-score, indicating the presence of a postoperative delirium, the Delirium Rating Scale-Revised-98 (DRS-R98)[11] was used to quantify the severity of the delirium and confirm the diagnosis. If the patients developed a delirium, standardized psychiatric treatment according to APA guidelines[24] was applied. Each day, details of the medical condition were recorded in separate files. Body fixation due to restlessness or uncontrollable behavior was quantified and specified by means of item 7 of the DRS-R98.

Wrist-actigraphy

To assess spontaneous 24-hr motor activity, the patients wore a wrist-actigraph continuously for 6 days. The non-dominant wrist was chosen as recording site, because it is assumed to be more reflective of movements of the total trunk and less of movements involved in performing specific tasks.[13,25]

The actigraph (Actiwatch, Cambridge Neurotechnology Ltd, Cambridge, UK) was set to count the number of supra-threshold movements per 1 min epoch lengths. The following motor activity parameters were computed per sequential nighttime (23.00 h – 06.00 h) and daytime period (06.00 h – 23.00 h): mean Activity per minute, based on the average activity score in those 1 minute epochs where scores of greater than 0 were recorded; number of minutes Immobile, based on the total number of minutes where a score of zero was recorded; and Restlessness Index, based on the addition of the percentage of time spent moving and the percentage immobility phases of 1 minute. In addition, we computed Activity Amplitude as the difference between the least active 5 h period and the most active 10 h period within each 24-hr period (starting at 19.00 h on the day of surgery).[16]

Amplitude data were used as an indicator of recovery of circadian rest-activity pattern. Activity per minute, number of minutes Immobile and the Restlessness Index were used to describe mean activity level, and duration of immobility and fragmentation of motor activity per nighttime and daytime period. From the 79 recordings that were made, 7 measurements could not be analyzed due to technical problems.

Questionnaires

The Confusion Assessment Method-Intensive Care Unit (CAM-ICU; Dutch translation: Vreeswijk et al).[22] In this study, a set of four items was used to asses the presence of a delirium. The items are based on the criteria for delirium based on the DSM-IV, and can be assessed rapidly (less than 5 min) by trained interviewers who can be non-clinicians. A positive diagnosis requires the presence of an acute onset and fluctuating course, as well as inattention, and either disorganized thinking or altered level of consciousness.[23] If the CAM-ICU score was positive, the DRS-R98 was also assessed.

The Delirium Rating Scale-Revised 98 (DRS-R98; Dutch translation: Sno and Van der Mast).[11] The DRS-R98 consists of 16 items: 13 severity items and three diagnostic items. It measures the broad constellation of delirium symptoms and generates a total severity score for delirium. The revised version integrates the DSM-IV criteria.[21] A special advantage is that the DRS-R98 is not purely based on cognitive impairment and thus allows an assessment of the interrelationships among the wide range of symptoms of delirium. Items are scored from 0-2 or 0-3 and cover the following symptoms: sleep-wake cycle disturbances, hallucinations, delusions, psychomotor behavior, language, thought processes, liability of affect, temporal onset, physical disorder, variability of symptoms and components of cognition.[11]

Statistical analysis

Although we focused on a measurement period of one week, we limited our analyses to the first 5 days because several of the patients were already moved to another hospital/ward after a postoperative period of 4 or 5 days depending on recovery speed or occurrence of complications. Normality of distribution of our parameters was established by means of Kolmogorov-Smirnov tests. In order to determine if recovery of motor activity parameters during the post-operative days was different for the three patient groups, Huynh-Feldt corrected ANOVA's for repeated measurements were performed with between-subject factor Group (Non-cr-Del, Short-Del, Sustained-Del), within-subject factor Time (5 sequential days or time points), and the interaction between factors Group and Time. In the case of a significant effect, post-hoc Scheffe tests were used to determine specific differences between groups. All analyses were performed with SPSS for Windows (version 11.0). A p-value of <0.05 was used to indicate a significant effect or difference.

RESULTS

Delirium severity

Delirium severity (DRS-R98) in the Short-Del group decreased, on average, from 24.8 (SD=10.3) on day 1 to 5 (SD=5.2) after 5 days. The Sustained-Del group only showed minor improvement of delirium severity from day 1 to day 5: from 19.1 (SD=8.7) to 16.3 (SD=10.5).

Motor activity parameters

Figure 1 illustrates individual actigraph characteristics of post-surgery recovery of 24-hr motor activity patterns in non-delirious and delirious patients. A gradual recovery of circadian rest-activity amplitude was apparent in the non-delirious patients (Fig. 1a). A peak of activity during the morning of these patients usually was associated with the habitual activities/routines of the hospital. Between 13.00 and 14.00 hrs, a daytime nap was customary. In the severe delirious patients, recovery of rest-activity patterns was less apparent or absent (Fig. 1b,c).

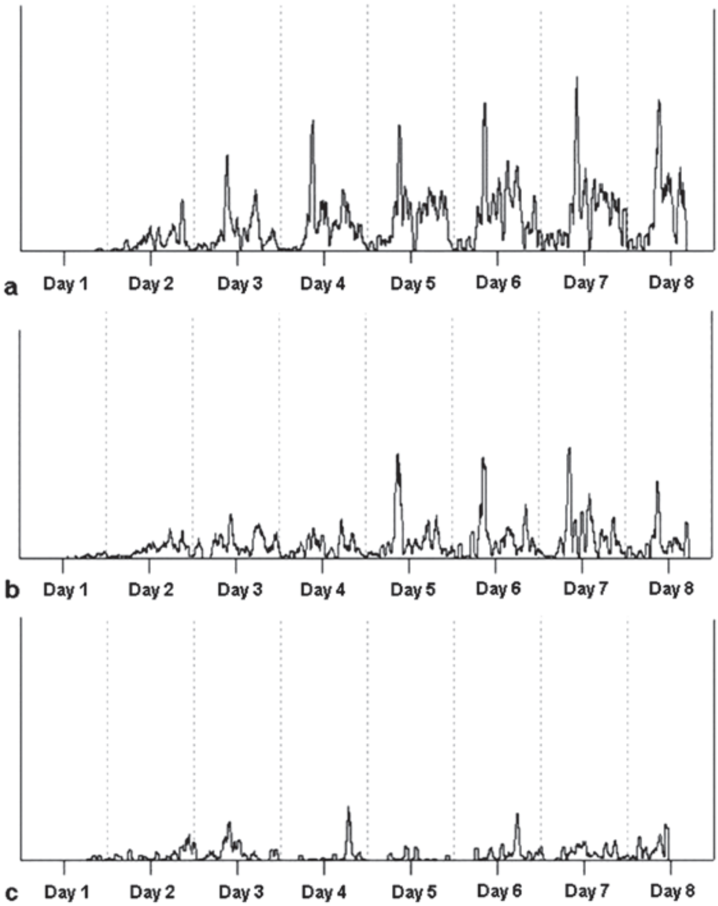

Figure 1. Recovery of the 24-hour motor activity pattern (presented with a 30 min smoothing factor) during a one-week period following cardiac surgery in: a) a non-delirious patient, b) a patient who was delirious for the first three postoperative days, and c) a patient who was delirious during the whole postoperative week.

Activity Amplitude

A significant effect was found for factors Group (F[2,63] = 3.3, *P* = 0.044), Time (F[2.5,157] = 29.5, *P* < 0.001), and the interaction effect between factors Group and Time (F[4.9,157] = 2.8, *P* = 0.019): during the five post-operative 24-hr periods, mean Amplitude levels were overall higher for the Non-cr-Del group and the Short-Del group, and increased more in these groups as compared to the Sustained-Del group (Table 1).

Table 1: Mean (SD) values of motor activity parameters during five sequential nighttime periods (23.00-06.00 h)), as well as the activity amplitude of the five sequential 24-hr periods, in postoperative delirium.

	Nights	Non-cr-Del	Short-Del	Sustained-Del
Mean Activity/min	1	7.4 (9.0)	4.2 (7.5)	9.8 (21.1)
	2	11.9 (11.9)	20.1 (24.3)	16.7 (15.3)
	3	18.3 (17.3)	22.4 (15.0)	14.9 (19.1)
	4	18.8 (15.4)	23.3 (24.7)	20.3 (18.8)
	5	23.5 (16.2)	27.0 (33.3)	23.7 (23.7)
Restlessness index	1	26.5 (19.3)	19.3 (22.4)	28.4 (42.3)
	2	35.8 (22.9)	51.8 (25.7)	48.3 (33.7)
	3	49.8 (23.7)	67.4 (30.7)	44.9 (28.9)
	4	47.4 (22.2)	49.4 (27.0)	57.9 (36.0)
	5	49.1 (21.8)	57.7 (31.5)	59.8 (29.5)
Immobility minutes	1	369 (45)	379 (54)	364 (104)
	2	345 (54)	308 (66)	318 (67)
	3	326 (58)	268 (75)	334 (73)
	4	325 (50)	311 (69)	291 (90)
	5	317 (52)	292 (87)	307 (82)
Amplitude	1	1842 (1396)	2030 (1660)	1310 (1117)
	2	3037 (2294)	2366 (2101)	1904 (1304)
	3	4249 (2682)	3644 (3647)	2657 (2307)
	4	5197 (2655)	5028 (3856)	2112 (1966)
	5	6288 (4042)	5833 (3688)	2785 (2557)

Non-cr-Del (Non-clinically relevant-delirium) Absent or first day delirious;
Short-Del (Short-delirium): 2 or 3 days delirious;
Sustained-Del (Sustained-delirium): 4 or more days delirious.

Night period analyses (Table 1)

Significant main effects of Time were found for Activity/minute ($F[3.5, 223.1] = 12.9$, $P < 0.001$), Restlessness index ($F[3.7,233.7] = 21.2$, $P < 0.001$), and number of Immobility minutes ($F[3.7,288.3] = 18.9$, $P < 0.001$), showing an increase in Activity/min and Restlessness index and a decrease in number of Immobility minutes over the five sequential postoperative nights, particularly from night 1 to night 2. No main effects for factor Group were observed. However, significant interaction effects between factors Group and Time were found for the Restlessness index ($F[7.8,233.7] = 2.1$, $P < 0.041$) and number of Immobility minutes ($F[7.4,228.3] = 2.2$, $P = 0.03$), which could be explained by an increase in Restlessness index and a decrease in number of Immobility minutes particularly during night 3 in the Short-Del group.

Day period analyses (Table 2)

For Activity/minute, significant effects for Group ($F[2,59] = 4.2$, $P = 0.02$), Time ($F[1.9,115.2] = 35.8$, $P < 0.001$), and the interaction effect between factors Group and Time ($F[3.9,115.2] = 2.5$, $P = 0.045$) were found: post-hoc analyses showed that Activity/minute overall was higher for the Non-cr-Del group and the Short-Del group and increased more during the five postoperative days in both groups as
compared to the Sustained-Del group. The Restlessness index showed a time-dependent increase (factor Time: $F[2.8,158.9] = 58.9$, $P < 0.001$), and was overall higher in the Non-cr-Del group and the Short-Del group (factor Group: $F[2,57] = 4.6$, $P = 0.014$) as compared to the Sustained-Del group (Table 2). Similarly, the number of Immobility minutes decreased significantly over time (factor Time: $F[2.4,140.6] = 43.7$, $P < 0.001$), and was overall lower for the Non-cr-Del group and the Short-Del group as compared to the Sustained-Del group (factor Group: $F[2,59] = 5.3$, $P = 0.008$).

Table 2. Mean (SD) values of motor activity parameters during five sequential daytime periods (06.00-23.00 h) in postoperative delirium.

	Days	Non-cr-Del	Short-Del	Sustained-Del
Mean Activity/min	1	32.9 (22.0)	39.8 (50.7)	27.0 (23.1)
	2	57.0 (36.7)	57.5 (68.4)	32.9 (24.3)
	3	79.9 (38.7)	68.2 (54.1)	34.3 (23.5)
	4	96.3 (35.2)	90.7 (63.6)	43.1 (32.7)
	5	109.5 (48.9)	104.3 (56.0)	58.3 (44.9)
Restlessness index	1	70.6 (27.1)	69.9 (25.6)	58.3 (29.9)
	2	88.7 (22.3)	94.4 (26.3)	74.1 (33.8)
	3	107.6 (20.7)	101.8 (22.8)	87.0 (29.0)
	4	113.9 (19.8)	111.2 (23.1)	88.6 (28.2)
	5	117.4 (19.1)	114.4 (23.6)	92.8 (35.6)
Immobility minutes	1	615 (183)	639 (178)	721 (187)
	2	528 (157)	496 (184)	615 (211)
	3	412 (134)	431 (160)	583 (195)
	4	372 (123)	392 (184)	542 (195)
	5	340 (126)	362 (183)	507 (225)

Non-cr-Del (Non-clinically relevant-delirium) Absent or first day delirious;
Short-Del (Short-delirium): 2 or 3 days delirious;
Sustained-Del (Sustained-delirium): 4 or more days delirious.

Body fixation

Body fixation (chest and wrist fixation) did not occur in the Non-cr-Del group, and was applied only once in one patient of the Short-Del group during the first post-operative day. In the Sustained-Del group, body fixation occurred in one patient during day 1, in two patients during day 2, three patients during day 3, one patient during day 4, and was not applied during day 5.

DISCUSSION

In order to objectively quantify characteristics of 24-hr motor activity patterns after cardiac surgery, wrist-actigraphy was explored during a 5-day postoperative period in patients who did or did not develop a postcardiotomy delirium. All patients tolerated wrist-actigraphy well and showed no signs of discomfort. The activity Amplitude, the daytime Activity/minute, as well as the daytime Restlessness index were found to be significantly higher for the patients in which delirium was absent or with short delirium episodes (≤ 3days), and to increase more during the subsequent days in these groups as compared to patients with sustained delirium episodes (≥ 4 days). The daytime number of Immobility minutes was significantly lower for the patients without delirium or with short-lasting delirium episodes, as compared to the patients with longer lasting delirium episodes. Overall, night-time motor activity did not show a clear differentiation between the three groups, when considering the whole postoperative 5-day period.

We observed a clear time-dependent increase in activity Amplitude in the patients with no delirium or a non-clinically relevant postoperative delirium, reflecting a gradual normalization of circadian rest-activity patterns associated with physical recovery and increase of daytime mobility. Although Activity/min during the five sequential nights increased significantly, particularly from night 1 to night 2, the gradual increase in activity Amplitude was primarily caused by an increase in mean daytime Activity, accompanied by less Immobility minutes and a higher Restlessness index. Typical hospital routines of daytime activities and naps were clearly reflected in the individual rest-activity patterns. Yet, variability of all our motor activity parameters was high, in all patient groups. Large inter-individual differences also exist in 24-hr motor activity patterns of healthy subjects, which, among others, may reflect influences of age, gender, job-related activities, and personality.[26,27] In this study, the measurement environment and daily routines were similar for all subjects, and the subjects were 65 years or older. Inter-individual differences in pre-surgery activity level and physical condition, and daily fluctuations in severity of illness, medical complications, and medication use may all have contributed to the high variability, irrespective of the presence of a delirium.

We studied actigraphy in relation to the duration of the delirium. A brief delirious episode frequently occurs as a result of the recovery from the anaesthesia; in general this period is considered to be too short to justify the clinical diagnosis of a postoperative delirium. Yet, in future research, it may be relevant to separate these two groups, in order to discover potential differences in the initial recovery phase directly after surgery. Wrist-actigraphy has been shown to be sensitive to effects of depth of anesthetics and sedation.[20]

In this study, we made no distinction between subtypes of delirium, but focused on the duration of the delirium instead. Because the diagnosis of the subtype of delirium may fluctuate on a daily basis (based on daily DRS-R98 assessments), we chose to study recovery of circadian rest-activity patterns in relation to duration of the delirium episode first. Approximately half of all delirium patients showed a hypoactive-hypokinetic subtype of delirium, with diminished attention, slowed speech and thought and lack of activity. Only two patients displayed a hyperactive-hyperkinetic subtype of delirium. The remaining delirium patients showed a mixed subtype with predominant inactivity and limited periods of restlessness. Between the patient groups experiencing a short or sustained delirious episode, there were no differences in clinical presentation apart form duration of the symptoms.

It is our current impression that DRS-R98 ratings emphasize isolated incidences of restlessness or uncontrollable behavior in subtyping the delirious patients as hyperactive or mixed (because these incidences draw the attention of clinicians and nurses), whereas wrist-actigraphy emphasizes overall patterns of rest and activity. In a larger sample, characteristics of the hyperactive, hypoactive, and mixed subtypes of delirium based on quantification by the DRS-R98 are interesting to analyze in relation to specific actigraphy parameters. Presently, our data indicate that, dependent upon the duration of the delirious episode, recovery of circadian rest-activity patterns is severely diminished in postcardiotomy delirium.

Limitations of the study

1. Possible limitation of body movement due to body fixation, and the presence of drains, intravenous lines or intubation: wrist-actigraphy data can be influenced by restriction of body/limb movement due to these factors. In our sample, body fixation occurred only a limited number of times in the delirious patients, on isolated instances of different days in different patients, and primarily in the group with sustained delirium episodes. Although a minor influence of body fixation on our results can not be excluded, it seems highly unlikely that body fixation can explain the lack of recovery of circadian rest-activity patterns in the patients with a sustained delirium (episode > 3 days). The presence and duration of intubation, drains or intravenous lines was unfortunately not recorded in this study.
2. Drug treatment: recovery of circadian rest-activity patterns may be influenced by the specific drug treatment received by the delirious patients. All delirious patients received haloperidol for treatment of their delirious state. The treatment strategy was similar for all patients: a daily dose of approximately 2 mg haloperidol, was titrated to the lowest effective dose for each patient, meanwhile avoiding extra-pyramidal side-effects as long as the symptoms of the delirium were present. With clinical recovery, the haloperidol dose was slowly diminished (about 1 mg per day). Because of this strategy

and the estimated brain half-life time of haloperidol being 6.8 days,[28] it is unlikely that the difference in recovery of circadian motor activity patterns between the patients with a short (≤ 3 days) and sustained (≥ 4 days) delirium that we observed within a 5-day postoperative period can be explained by the treatment with haloperidol. This assumption is supported by the study of Kiang *et al.*,[29] who failed to find a significant change in actigraphic motor activity between placebo and one dose of 2 mg haloperidol in healthy subjects. Nevertheless, future research should address this issue in more detail. Apart from the specific treatment with haloperidol, it is clear that all the patients used a large number of different drugs during and after cardiac surgery. The influence of specific classes of drugs, particularly of narcotics, analgetics, and benzodiazepines, on the motor activity pattern needs to be evaluated in a larger sample of patients.

IN CONCLUSION

Disturbance of motor rest-activity patterns is an important clinical symptom of postcardiotomy delirium. Objective quantification of motor characteristics, beyond the clinical assessments by means of questionnaires, may have relevance for diagnostic purposes, for early recognition of subtypes of delirium, which may improve prognosis by early treatment, and for the development and evaluation of treatment strategies. Our data show that wrist-actigraphy is an unobtrusive method to objectively quantify recovery of 24-hr rest-activity patterns after cardiac surgery.

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3

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Chapter

4

Screening methods for delirium: early diagnosis by means of objective quantification of motor activity patterns using wrist-actigraphy

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ABSTRACT

Objective Delirium after cardiac surgery is a risk factor for adverse outcome and even death. Disturbance of motor activity is a core feature of delirium, but hypoactive delirium often remains unrecognized. We explored wrist-actigraphy as a tool to objectively quantify postoperative recovery of 24-hour rest-activity patterns to improve the early recognition of delirium after surgery.

Methods Motor activity was recorded by wrist-actigraphy after cardiac surgery in 88 patients over 65 years of age. Patients were assessed daily by using the CAM-ICU. Our final analyses were based on 32 non-delirious patients and 38 patients who were delirious on the first day after surgery.

Results The delirious patients showed lower mean activity levels during the first postoperative night ($P < 0.05$), reduced restlessness during the first day ($P < 0.05$), and a lower mean activity of the 5 h with lowest activity within the first 24 h ($P = 0.01$) as compared to the non-delirious patients.

Conclusions Already at a very early stage after cardiac surgery, a difference in motor activity was observed between patients with and without a delirium. As an unobtrusive method, actigraphy has the potential to be a screening method that may lead to early diagnosis and treatment of delirium.

Keywords: Delirium, Postcardiotomy, Actigraphy, Motor activity, Motor subtypes

INTRODUCTION

Delirium after surgery, particularly in elderly patients, is an independent risk factor for adverse outcome and even death [1]. It is unfortunate that it is still poorly recognized, especially the hypoactive subtype [2]. Complex issues are involved in relation to validity of diagnostic tools [3]. The most frequently used diagnostic tools for delirium, such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [4] and the Delirium Rating Scale - Revised '98 (DRS-R98) [5], may improve detection, but require training and can provide ambiguous results. In addition, prophylactic use of haloperidol has been shown to reduce the severity and duration of delirium in geriatric patients [6]. However, although prophylactic use of haloperidol may improve outcome in general, it leads to unnecessary treatment of 68 - 77% of the elderly patients after cardiac surgery [7,8]. An objective and easy to use tool for the early detection of delirium is desirable.

Considering the clinical importance of disturbed motor activity patterns in a delirium after cardiac surgery, quantification of motor activity patterns seems an obvious choice. Wrist-actigraphy can be used as an objective method to assess 24-h patterns of spontaneous motor activity for prolonged periods of time. The method accurately distinguishes rest from activity periods in a valid and reliable way [9]. In a variety of psychiatric and neurological patient categories, wrist-actigraphy has been used to quantify disturbances in sleep-wake schedule, alterations in diurnal rest-activity patterns, as well as psychomotor disturbances (psychomotor retardation or agitation) (e.g. [10]).

We explored the usefulness of wrist-actigraphy to improve the early recognition of delirium after surgery by focusing on the (circadian) motor activity patterns during the first night and day following cardiac surgery.

MATERIALS AND METHODS

Subjects

We studied 88 patients of 65 years and older who underwent elective cardiac surgery at the department of Cardiothoracic Surgery of the Erasmus Medical Center. Patients were excluded from the study if they required emergency surgery, showed signs of pre-existing delirium, or were unable to speak sufficient Dutch or could not provide written informed consent. In addition, subjects were excluded if they were comatose on day 1 (n=5) or diagnostic assessments could not be made (n=6). Due to technical problems with the actigraph (n=5) or sudden discharge from the hospital (n=2), the data of another seven patients were lost for evaluation. As such, 70 subjects were included in our analyses.

The study protocol was approved by the Medical Ethical Committee of the Erasmus MC and conducted in accordance with the criteria of Good Clinical Practice (Declaration of Helsinki, 2004).

Procedure

The patients underwent elective cardiac surgery (coronary artery bypass graft, valve surgery, or both) at the department Cardiothoracic Surgery of the Erasmus Medical Center in Rotterdam. Eligible patients were invited to participate in the study after having received detailed information in both oral and written form. All patients provided written informed consent before entering the study.

Surgery was scheduled at variable times during the day; however, most patients were operated on during the morning. As soon as the patients returned from surgery to the intensive care unit (usually in the afternoon; day 0), the actigraph was placed on the non-dominant wrist for continuous measurement of 24-h motor activity patterns.

The data presented in this study are limited to the first postoperative night and day. Daily, between 9.00 and 12.00 h, the diagnosis delirium was assessed and evaluated daily by a senior psychiatrist and/or trained researchers based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [11] and the four-item diagnostic Confusion Assessment Method-Intensive Care Unit (CAM-ICU) algorithm. A positive diagnosis requires the presence of an acute onset and fluctuating course, as well as inattention, and either disorganized thinking or altered level of consciousness [4]. In this pilot study, we used the CAM-ICU score of the first day to define our subgroups of delirious and non-delirious patients.

If the patients developed a delirium, standardized psychiatric treatment according to APA guidelines was applied in all delirious patients [12]. Each day, details of the medical condition, including body fixation, and possible adverse reactions of the patients towards the use of the actigraph were recorded in separate files.

Wrist-actigraphy

To assess spontaneous 24-h motor activity, the patients wore a wrist-actigraph continuously for six days on the non-dominant wrist. The non-dominant wrist is more reflective of movements of the total trunk and less of movements involved in performing specific tasks [9]. The Actiwatch® actigraph (Cambridge Neurotechnology Ltd, Cambridge, UK) (size 27 x 26 x 9 mm; weight 16 g) contains a piezo-electric acceleration sensor and counts the number of supra threshold movements (> 0.05 g acceleration) per 1 min epochs lengths. The following motor activity parameters were computed per nighttime (23.00 h – 06.00 h) and daytime period (06.00 h – 23.00 h): mean Activity per minute (the average activity score in those 1 min epochs where scores of > 0 were recorded); number of minutes Immobile (the total number of minutes where a score of zero was recorded); and Restlessness Index (the addition of the percentage of time spent moving and the percentage immobility phases of 1 min). In addition, the mean activity of the 5 h with the least activity (L5) and the 10 h (M10) with the highest activity within the first 24-h period were analyzed to evaluate more sustained periods of (in)activity independent of clock-time, reflecting circadian rhythm disturbances [10].

Statistical methods

Differences between the surgical characteristics of the delirious and non-delirious patients were evaluated by means of *t*-tests, with the exception of lowest body temperature (Mann-Whitney *U*-test, due to skewness of the distribution). The activity parameters during the first postoperative night and day period were all not normally distributed (Kolmogorov-Smirnov tests). Therefore, data are presented in median (minimum, maximum) values; Mann-Whitney *U*-tests were performed to evaluate differences between delirious and non-delirious patient groups. All analyses were performed with SPSS for Windows (version 16.0). A $P < 0.05$ was used to indicate a significant difference.

RESULTS

Patient and operation characteristics

The percentage of males and females was similar for both groups, whereas mean age was significantly higher for the delirious patient group as compared with the non-delirious patient group (Table 1).

Table 1. Demographic and surgical characteristics of non-delirious and delirious patients.

	Non-delirious	Delirious	T/Z-value; *P*-value
n	32	38	
Males / Females (n/n)	16/16	19/19	
Age in years mean, (SD)	73.0 (4.6)	76.0 (4.9)	-2.56; 0.01
Type of surgery (N; %)			
CABG	12 (38 %)	13 (34 %)	
AVR	10 (31 %)	8 (21 %)[1]	
AVR + CABG	5 (16 %)	7 (18 %)[2]	
MVP	3 (9 %)[3]	4 (11 %)	
MVP + CABG	1 (3 %)	4 (11 %)	
AVR + MVP (+CABG)	1 (3 %)[4]	2 (13 %)[5]	
Duration surgery (min) mean (SD)	260 (63)	310 (93)	-2.63; 0.01
ECC time (min) mean (SD)	134 (44)	163 (61)	-2.17; 0.03
AoX time (min) mean (SD)	89 (34)	107 (43)	-1.95; 0.06
Lowest body temperature (ºC) mean (SD)	30.9 (1.5)	29.8 (3.3)	-1.13; ns

AVR: aorta valve replacement; CABG: coronary artery bypass graft; MVP: mitral valve plasty; ECC time: extra corporal circulation time; AoX time: aorta crossclamp time.
[1] Including 2 Bentall procedures; [2] Including 1 Bentall procedure; [3] Including 1 tricuspid valve annuloplasty;
[4] AVR + MVP, [5] AVR + MVP + CABG, including 1 tricuspid valve annuloplasty; ns: non-significant.

With the exception of mitral valve plasties in combination with coronary artery bypass graft surgery and Bentall procedures (which were more common in the delirious group), the types of surgery were overall equally distributed between the two groups.
The duration of the surgery and the extra corporal circulation were significantly longer in the delirious group as compared to the non-delirious group (Table 1). The duration of aorta crossclamp time showed a trend ($P = 0.06$) towards a significant increase in the delirious patients. The lowest body temperature during surgery was also not significantly different between the delirious and non-delirious groups.

Illustrative actigraphy examples

Figure 1 illustrates individual actigraph characteristics of post-surgery recovery of 24-h motor activity patterns in a non-delirious patient (Fig. 1a) and a delirious patient (Fig. 1b). A gradual recovery of 24-h rest-activity periodicity was usually apparent in the non-delirious patients. In the severe delirious patients, recovery of rest-activity patterns was less apparent.

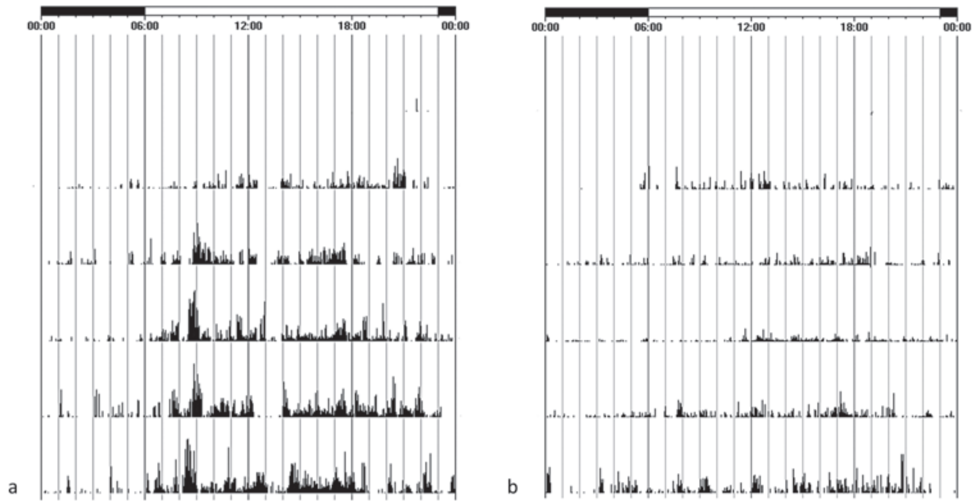

Figure 1. Examples of wrist-actigraphy recordings (based on 1 min epoch lengths) during a post-surgery recovery period of six days of a non-delirious patient (a) and a delirious patient (b). Each line indicates a 24-h period, starting at midnight. The black bars mark the analyses periods for the nights (23.00 h – 6.00 h). The recordings started at 21.00 h (a) and 18.00 h (b), respectively. Daytime naps between 13.00 and 14.00 h are apparent in the non-delirious patient.

Motor activity during first post-operative night and day

The delirious patients showed a significantly lower mean activity level during the first postoperative night, and a significantly reduced restlessness during the first postoperative day, in comparison with non-delirious patient group (Table 2). Also, the mean activity of the 5-h period with lowest activity within the first 24 h was significantly lower in the delirious patients as compared to the non-delirious patients (Table 2). Two trend-effects were observed regarding motor activity during the day-period: the number of immobility minutes was higher and mean activity level was lower for the delirious group as compared to the non-delirious group (P = 0.09 and P = 0.08, respectively).

Body fixation (chest and wrist fixation) did not occur in the non-delirious group, and was applied twice for a short period of time in two patients of the delirious group during the first post-operative day to prevent self-harm.

Table 2. Median (Minimum, Maximum) values of the motor activity parameters during the first post-operative night and day.

	Non-delirious	Delirious	Z-value; *P*-value
Immobility			
Night 1	371 (222, 420)	395 (22, 420)	-1.61; ns
Day 1	632 (239, 863)	732 (50, 925)	-1.70; 0.09
Mean activity			
Night 1	5 (0, 47)	2 (0, 80)	-1.97; 0.05
Day 1	32 (9, 92)	25 (3, 200)	-1.77; 0.08
Restlessness			
Night 1	25 (0, 82)	21 (0, 162)	-1.07; ns
Day 1	73 (33, 130)	53 (11, 125)	-2.13; 0.03
L5	172 (0, 2431)	14 (0, 2523)	-2.53; 0.01
M10	2065 (549, 6969)	1712 (226, 5498)	-1.24; ns

L5, mean activity of the 5 h with the lowest activity within the first 24 h;
M10, mean activity of the 10 h with the highest activity within first 24 h;
ns, non-significant.

DISCUSSION

Our data illustrate that at a very early stage after cardiac surgery, a difference in behaviour can be measured between patients with and without delirium. The delirious patients showed lower mean activity levels during the first post-operative night, and a reduced restlessness during the first day, compared to non-delirious patients.

Wrist-actigraphy was well tolerated by all patients. In comparison with other techniques to objectively measure movement, such as video monitoring and more complex accelerometry techniques, wrist-actigraphy is easy to use and has little influence on the privacy of the patients.

Increased or decreased psychomotor activity and a disturbed sleep-wake cycle are among the key symptoms of delirium [13]. A distinction is usually made between hyperactive, hypoactive or mixed subtypes of delirium, with presumed differences in underlying pathophysiology and response to treatment [3]. The hypoactive subtype of delirium is usually poorly recognized, partly because the clinical ratings emphasize isolated incidences of (nighttime) restlessness or uncontrollable behavior (because they draw the attention of clinicians and nurses). Changes in the circadian rhythm are among the most often present symptoms in delirium [11]. Our preliminary data show that reduced motor activity may be a much more prevalent feature of delirium than presently assumed, at least during the first post-operative night and day.

Possible limitations of this study are that the results may reflect the characteristics of our elderly patient group (based on DRS-R98 analyses, the majority of patients were hypoactive, 53%, or mixed, 35%). Parts of the results may be due to the administration or persistent effects of opiates and sedatives during this initial postoperative period. Also, the standardized treatment of a delirium with haloperidol may have influenced our measurements, although no significant changes on actigraphic measures were found in a study using comparable doses of haloperidol in healthy volunteers [14].

This study focused on early recognition of delirium; we used the CAM-ICU records of the first day after surgery to attribute the patients to either the delirious or non-delirious group. As a consequence, the group of delirious patients contained patients with durations ranging from one to more days. Because a delirium is an indicator of underlying serious problems and is associated with severe complications, there is clinical support for this choice.

In agreement with other authors, we found that longer duration and higher complexity of surgery were associated with a higher chance of experiencing a delirium after surgery [e.g. [8]]. Further research should clarify to which extent processes such as micro-emboli, inflammatory processes (e.g. cytokine activation) or arteriosclerotic changes in the brain, pre-existing psychiatric or neurological disorders, genetic influences, differences in specific surgical (such as deep-cooling) or anesthetic techniques, drug use or other frailty factors contribute to the measured motor differences between the two groups.

Variability of all our motor activity parameters was high in both groups of elderly patients, but particularly in the delirious group, reflecting potential influences of age, pre-surgery activity level and physical condition, as well as daily fluctuations in severity of illness, medical complications and medication use, body fixation, and the presence of drains or intubation. A larger study is necessary to unravel the contribution of each of these factors to recovery of motor activity patterns, in relation to the presence of a delirium. In such a study, the potential of the method to actually predict delirium should also be addressed, to evaluate the possibility to obtain clear cut-off points beyond which the risk of delirium would justify prophylactic treatment in specific patients.

CONCLUSION

Disturbance of motor activity patterns is an important clinical manifestation of a delirium after cardiac surgery. Our data show that already at a very early stage after cardiac surgery, a difference in motor activity was observed between patients with and without a delirium. As an unobtrusive method, actigraphy has the potential to be a screening method that leads to early diagnosis and treatment of delirium.

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Chapter

5

High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults

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ABSTRACT

Objectives To examine the association between plasma levels of pterins and amino acids and postoperative delirium.

Design Prospective cohort study.

Setting Cardiothoracic services in a university hospital in Rotterdam, the Netherlands.

Participants One hundred twenty-five individuals aged 70 years and older undergoing elective cardiac surgery.

Measurements Plasma pterins and amino acids were measured pre- and postoperatively. Using multiple logistic regression analyses, the associations between pterins and amino acid levels and postoperative delirium were examined in relation to age, sex, comorbidity, cognitive functioning (Mini-Mental State Examination (MMSE) score), and cardiac risk factors.

Results The delirium incidence in the main study group was 31.3 %. The preoperative measures associated with delirium were neopterin (Odds ratio (OR) = 1.05, $P = 0.009$), MMSE- score less than 28 (OR = 4.39, $P = 0.001$), European System for Cardiac Operative Risk Evaluation score greater than 6 (OR = 2.84, $P = 0.03$), and combined coronary artery bypass graft (CABG) and aortic, mitral, or tricuspid valve surgery (OR = 4.32, $P = 0.01$). The postoperative measures associated with delirium were neopterin (OR = 3.84, $P = 0.02$), homovanillic acid (HVA, OR = 1.01, $P = 0.04$), and preoperative MMSE-score less than 28 (OR = 3.32, $P = 0.008$).

Conclusions Preoperatively high neopterin levels predicted delirium after cardiac surgery in older adults, in addition to the well-known risk factors of poor cognitive function, high cardio-surgical risk and combined CABG and valve surgery. Postoperative neopterin and HVA levels were also found to be associated with delirium, together with preoperative cognitive functioning. Plasma neopterin may be a candidate biomarker for delirium after cardiac surgery in these older adults.

Keywords: Delirium, Cardiac surgical procedures, Immune activation, Neopterin, Amino acids.

INTRODUCTION

Delirium is an acute neuropsychiatric syndrome, characterized by disturbances of attention and other cognitive functions (DSM-IV-TR) [1]. In older patients undergoing cardiac surgery, the incidence of postoperative delirium is reported to range from 30% to 52% [2,3]. Delirium is associated with serious adverse outcomes, including hospital complications, longer hospital stay, greater risk of posthospital institutionalization and cognitive dysfunction, poorer quality of life, and greater mortality [4]. Although several clinical risk factors for delirium have been well established [5], the pathophysiological pathways leading to delirium remain largely hypothetical.

Immune activation, oxidative stress and disturbances of cerebral neurotransmitters due to serious illness and the process of aging have all been implicated in the pathogenesis of delirium [6,7].

Activation of the immune system by disease states such as infection, tissue damage, hypoxia, and atherosclerosis causes monocytes and macrophages to produce neopterin, cytokines and reactive oxygen species, which can be found in plasma, urine and cerebrospinal fluid in delirium [6-9]. Neopterin is regarded to be a marker of cellular immune activation and oxidative stress; its plasma levels reflect the amount of immune activation and oxidative stress [8]. Although high neopterin levels have been found to be associated with prognosis in ischemic heart disease, human immunodeficiency virus dementia, and other cerebral disorders, its role in delirium has not been studied [10-12]. Other measures of oxidative stress are plasma levels of the amino acid citrulline, and the ratio of citrulline to arginine, which are involved in the formation of nitric oxide, an oxygen radical (reactive oxygen species), in a reaction using tetrahydrobiopterin (BH4) as an essential co-factor [13,14].

Disturbances of several cerebral neurotransmitters are also related to the development of delirium. It has been postulated that high rates of dopaminergic, noradrenergic or both neurotransmission and low rates of serotonergic neurotransmission cause delirium after cardiac surgery, based on the findings of a high preoperative ratio of phenylalanine to the other large neutral amino acids (LNAAs) and a low ratio of tryptophan to LNAAs in individuals who became delirious after cardiac surgery [15, 16]. Because dopamine and norepinephrine are synthesized from the amino acid precursors tyrosine and phenylalanine, in chemical reactions involving BH4 as essential cofactor, a deficiency of BH4 could be the underlying biochemical mechanism of these findings. In addition, BH4, as essential cofactor, mediates the synthesis of serotonin from its precursor tryptophan [17]. These amino acids enter the brain using the LNAA transporter protein. Because of the greater affinity of phenylalanine for the LNAA transporter protein, brain levels of phenylalanine can increase at the expense of the other LNAAs, such as tryptophan, possibly changing the levels of synthesis of the involved neurotransmitters [18].

The present study examined the association between pre- and postoperative levels of plasma pterins, amino acids, and HVA levels and delirium after cardiac surgery. It was hypothesized that high preoperative immune activation and oxidative stress, as reflected by high plasma levels of neopterin and citrulline and a high ratio of citrulline to arginine, would be associated with the development of a postoperative delirium. A previous study [16] that postulated that preoperative levels of the cerebral neurotransmitters dopamine and norepinephrine are high and the level of serotonergic neurotransmission is low in individuals with delirium after cardiac surgery was replicated. These changes in cerebral neurotransmitters would be reflected in higher ratios of tyrosine to LNAA or phenylalanine to LNAA and a lower ratio of plasma tryptophan to LNAA in individuals with delirium than in those without. The measurement of BH4 level was included in the analysis because a deficiency in this essential cofactor could diminish the synthesis of the relevant neurotransmitters. Finally, the plasma levels of HVA were measured, reflecting another estimation of the dopaminergic neurotransmission. Because known risk factors for delirium (age, comorbidity, severity of the disease, and cognitive functioning) might influence the findings, they were included in the analyses [19].

METHODS

Participants

Two hundred one individuals aged 70 and older who underwent elective cardiac surgery at the Department of Cardiothoracic Surgery, Erasmus MC (Rotterdam, the Netherlands) were included in this prospective cohort study between April 2005 and April 2008. Individuals undergoing coronary artery bypass graft (CABG) or valve surgery or both, were eligible to participate. Individuals in whom deep cooling, circulatory arrest, or emergency surgery was required or those who had insufficient understanding of the Dutch language were excluded. Preoperative delirium and insufficient adherence to the protocol were additional exclusion criteria.

All participants received verbal and written information and provided written informed consent before entering the study. The medical ethics committee of the Erasmus MC approved the study, which was conducted in accordance with the Declaration of Helsinki [20] and the Dutch legal regulations for studies on human subjects.

Assessments and procedure

Before surgery, sociodemographic data, current medical status, medication use, and the medical and psychiatric history were recorded for all participants. The day before surgery, global cognitive functioning was assessed using the Mini-Mental State Examination (MMSE) [21]. Preoperative anxiety and depression levels were measured using the Hospital Anxiety and Depression Scale (HADS) [22]. To ensure that none of the participants was delirious before surgery, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [23], which uses the definition of delirium according the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, was used. The thoracic surgeons used the European System for Cardiac Operative Risk Evaluation (EuroSCORE), a validated risk scale consisting of 17 risk factors influencing cardiac surgical outcome and mortality, to assess the baseline cardiac risk factors and the predicted operative mortality [24]. The severity of comorbidity was assessed using the Charlson Comorbidity Index, which was based on self-report by the participants and checked with the available medical records [25].

After surgery, a senior psychiatrist or trained researchers conducted delirium assessments between 10:00 a.m. and 12:00 p.m. daily using the CAM-ICU. Delirium lasting 2 days or longer according to the CAM-ICU criteria was considered clinically relevant and was therefore used as the grouping condition. The first day after surgery was not taken into account because of possible extended effects of anaesthesia. The daily assessments were performed until the participant was discharged from the hospital or until 7 days after surgery.

The pre- and postoperative biochemical analyses were based on blood samples collected on the day before and the second day after surgery.

Biochemical measurements

On the day before surgery and the second day after surgery, venous blood samples were drawn using ethylenediaminetetraacetic acid (EDTA) tubes. For measurement of BH4, EDTA tubes containing 0.1% (w/v) dithiothreitol (a potent reducer) were used to prevent oxidation of BH4 [26]. After the blood was centrifuged for 20 minutes at 2,650 g and 20°C, plasma was separated and stored at -80°C until data collection was complete. Amino acids were determined using high-performance liquid chromatography (HPLC), as previously described [27]. Total neopterin was measured by HPLC after acid oxidation [28]. Using this method, neopterin and dihydroneopterin that is oxidized to neopterin are measured together, resulting in levels approximately twice as high as the level of neopterin alone measured without acid oxidation. The reference value of plasma neopterin used for age-matched (74.5 ± 12.2) healthy persons was 21.3 ± 7.3 nmol/L (range 11 - 40 nmol/L). Total biopterin and BH4 were determined as described previously [26]. HVA was analysed using HPLC and electrochemical detection [29].

Statistical analysis

Univariate associations between participant characteristics and postoperative delirium were analysed using standard statistical tests. Unadjusted (crude) odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. In the case of a nonlinear relationship between predictor and outcome, dichotomization was performed using the mean or median value of group without delirium for the cut-off value. Sensitivity analyses were conducted to explore the effect of alternative dichotomizations. Multiple logistic regression analyses were performed using stepwise forward and backward procedures, with 0.25 and 0.05 alpha levels for entry and removal, respectively. The stepwise multiple logistic regression analyses included the biochemical variables BH4, total biopterin, and HVA; the ratios of tryptophan to LNAA, tyrosine to LNAA, phenylalanine to LNAA, phenylalanine to tyrosine, citrulline to arginine and taurine to serine times methionine (TSM ratio); baseline levels of C-reactive protein, plasma urea and Creatinine; and the demographic or risk factors age, sex, type of surgery, acute cardiac surgical risk factors (EuroSCORE), preoperative cognitive functioning (MMSE), preoperative anxiety and depression (HADS-subscales), and chronic medical comorbidity (Charlson Comorbidity Index). All significant main factors were checked for collinearities and interaction effects. Model selection was based on likelihood ratio test statistics. The fit of the final model was assessed using Nagelkerke R^2, Hosmer-Lemeshow goodness-of-fit tests, and the area under the receiver operating characteristic curve. SPSS for Windows version 17.0 (SPSS, Inc., Chicago, IL) was used to perform all statistical procedures.

RESULTS

Participant Characteristics

During the inclusion period, 369 participants met the inclusion criteria for the study and were asked to participate (Figure 1). One hundred sixty-eight participants were excluded – 162 because of refusal to provide informed consent. No significant differences were found in sex distribution or types of surgery between the 201 participating and 168 non-participating individuals, but participants were significantly older than those not participating (median 76.0 versus 74.0, $P < 0.01$). After cardiac surgery, 63 of the 201 participants became delirious, a delirium incidence of 31,3%.

To measure levels of pterins and amino acids, a nested sample of 130 participants was taken from the 201 participants in the main study. This sample consisted of all 63 participants with delirium and a randomly selected group of 67 control participants. Five participants from the delirious group were excluded because of missing neopterin data (n=4) or emergency surgery (n=1, with an extreme high neopterin value: 221.32 nmol/L). Further analyses were based on the remaining 125 participants.

Significant preoperative differences were found between participants with and without delirium in age ($P < 0.01$), MMSE-score ($P < 0.001$), EuroSCORE values ($P < 0.001$) and HADS depression subscale scores ($P = 0.05$) (Table 1). The potential confounders CRP ($P = 0.01$), creatinine ($P = 0.02$), and urea ($P = 0.02$) were also significantly higher preoperative, in the participants with delirium.

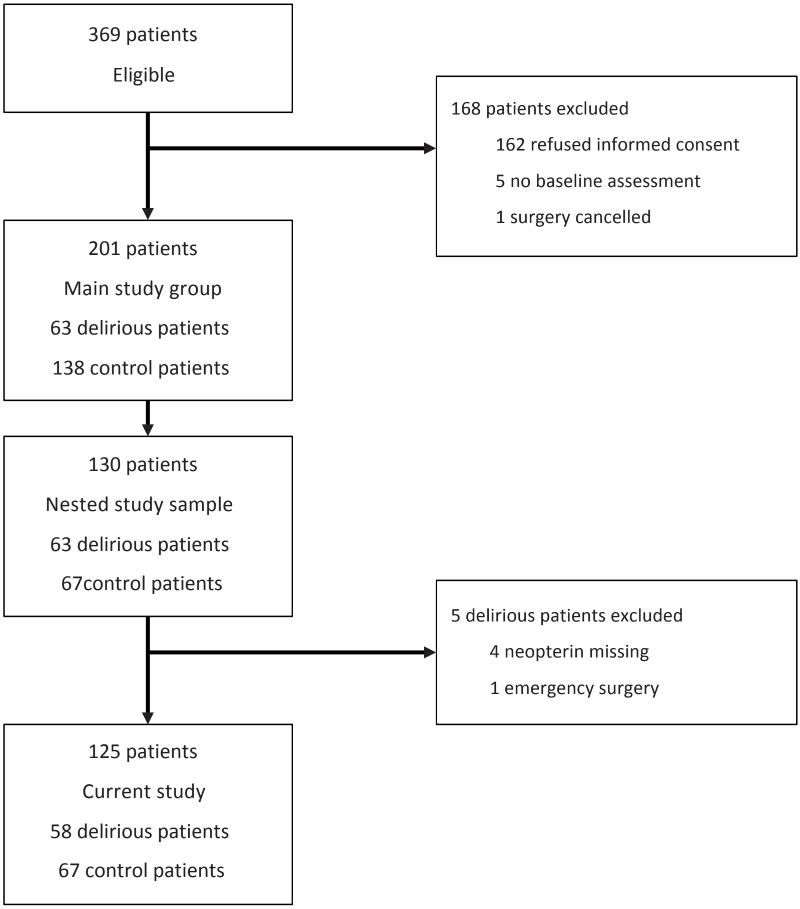

Figure 1. Flowchart of study inclusion.

Preoperative analyses

In univariate logistic regression analysis, the preoperative plasma levels of neopterin and HVA were significantly higher in the participants with delirium than in those without (both $P < 0.001$, Table 2, Figure 2). In addition, ratio of phenylalanine to LNAA ($P = 0.002$) and levels of citrulline ($P = 0.01$) and TMS ($P = 0.05$) were significantly higher in the participants with delirium. No significant differences between the preoperative BH4 levels and ratios of tryptophan to LNAA and tyrosine to LNAA were found between the two groups.

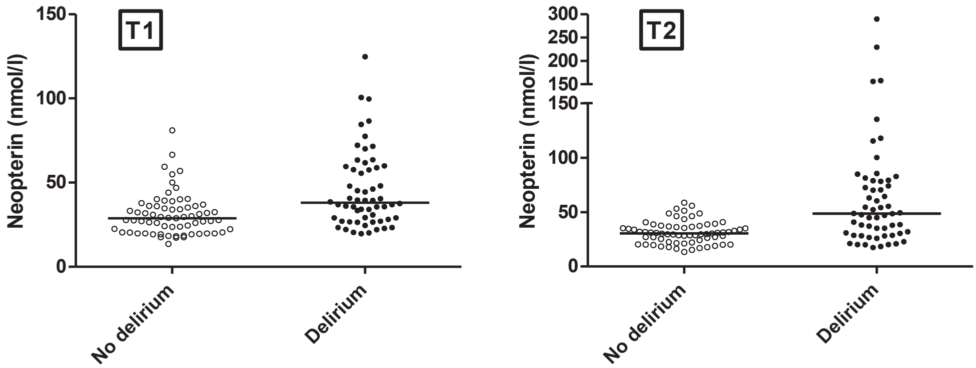

Figure 2. Scatter plots of preoperative (T1) and postoperative (T2) plasma neopterin levels.

Multiple logistic regression analysis was used to determine whether participants with higher preoperative neopterin levels were more likely to develop delirium after correction for demographic variables and risk factors. Because a linear relationship between delirium and preoperative neopterin levels only existed above the reference value of 28.75 nmol/l, the neopterin levels below 28.75 nmol/l were set to 28.75 nmol/l and centered.

The final model of preoperative risk factors for delirium included preoperative neopterin and the risk factors type of cardiac surgery, MMSE-score, and EuroSCORE value (Table 3). The overall model fit was adequate (model chi-square 39.800, degrees of freedom (*df*) 5, $P < 0.001$; Hosmer & Lemeshow goodness of fit test: 6.431, *df* 7, $P = 0.490$; Nagelkerke R^2 0.364; and ROC curve 0.815, 95%CI = 0.741-0.890, $P < 0.001$). No collinearity or interaction effects were found.

The preoperative model shows that higher levels of neopterin before surgery were associated with greater risk of becoming delirious after cardiac surgery. Based on the beta (0.047), every 1-nmol/L increase in neopterin level is associated with a 1.05 times increase in delirium risk (e.g., a 20-nmol/l increase of the neopterin level is associated with a 2.56-times higher risk of delirium, a 30-nmol/l increase in neopterin is associated with a 4-times higher delirium risk). In addition, combined CABG and valve surgery, MMSE score less than 28, and EuroSCORE value greater than 6 were associated with 4.3, 4.4 and 2.8 times greater risk, respectively, of delirium.

Postoperative analyses

The change in neopterin levels between the pre-operative and postoperative measurement was significantly larger in the group with delirium than in that without (median change 5.33 nmol/L (range: -20.36-230.84 nmol/L) vs 0.58 nmol/L (range -31.29 – 23.68 nmol/L), P = 0.006).

Table 1. Preoperative characteristics of participants with and without delirium.

Characteristic	No Delirium (n=67)	Delirium (n=58)	Statistic	*P*-value
Male/female, n/n	48/19	34/24	Chi-square 1.794, *df* 1	0.18
Age, mean ± standard deviation	75.1 ± 3.1	76.7 ± 3.9	t -2.579, *df* 123	<0.01
CABG surgery, n (%)	34 (51)	21 (36)	Chi-square 5.277, *df* 2	0.07
Valve surgery, n (%)	24 (36)	20 (35)		
CABG and Valve surgery, n (%)	9 (13)	17 (29)		
Education, n				
< High school	11	18	Chi 4.457, df 2	0.11
High school	41	26		
> High school	15	14		
MMSE score, median (range)	28 (22-30)	27 (16-30)	U = 1227, Z = -3.60	<0.001
MMSE score < 24, n	4	9	Chi-square 2.103, *df* 1	0.15
HADS anxiety subscale, median (range)	6 (2-13)	7 (3-12)	U = 1545, Z = -1.84	0.06
HADS depression subscale, median (range)	3 (0-15)	4 (0-15)	U = 1521, Z = -1.96	0.05
Charlson Comorbidity Index, median (range)	1 (0-6)	2 (0-8)	U = 1583, Z = -1.83	0.067
EuroSCORE value, median (range)	6 (3-10)	7 (3-15)	U = 1241, Z = -3.52	<0.001
Unstable angina pectoris, n [1]	2	1		> 0.99
Myocardial infarction within 90 days, n [1]	4	5		0.73
Left ventricular dysfunction, n	5	6	Chi-square 0.063, *df* 1	0.80
Systolic pulmonary artery pressure > 60 mm Hg, n [1]	1	5		0.09
Extracardiac Arteriopathy, n [2]	6	6	Chi-square 0.000, *df* 1	> 0.99
Diabetes mellitus without complications, n	16	11	Chi-square 0.751, *df* 2	0.69
Diabetes mellitus with complications, n [3]	2	3		
Creatinine, µmol/L, median (range)	87 (40-211)	98 (63-270)	U = 1450, Z = -2.44	0.01
Urea, mmol/L, median (range)	6.4 (3.6-24.7)	7.7 (4.3-15.6)	U = 1032.5, Z = -2.37	0.02
C-reactive protein, mg/L, median (range)	2.0 (1.0-55.0)	4.0 (1.0-64.0)	U = 958.5, Z = -2.53	0.01

[1] Statistical testing hampered or impossible because of low or zero values. [2] Claudication, carotid occlusion or > 50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids. [3] Diabetes Mellitus with neuropathy, nephropathy and/or retinopathy.
df = degrees of freedom; CABG = Coronary Artery Bypass Graft surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HADS = Hospital Anxiety and Depression Scale; MMSE: Mini-Mental State Examination; Valve surgery = Surgery on aortic, mitral or tricuspid valve.

Table 2. Pre- and postoperative pterins levels and amino acids plasma concentrations for participants with and without delirium.

	Preoperative measures (day before surgery)			*Postoperative measures (day 2 after surgery)*		
	No Delirium	**Delirium**		**No Delirium**	**Delirium**	
Pterins and Amino Acids	**n=67**	**n=58**	***P*-value**	**n=67**	**n=58**	***P*-value**
Neopterin, nmol/L, median (range)	28.75 (13.64-81.06)	38.07 (19.67-124.81)	<0.001	30.36 (13.36-58.55)	48.71 (17.36-289.67)	<0.001
Tetrahydrobiopterin, nmol/L, mean ± SD	7.58 ± 3.77	7.99 ± 3.68	0.60	5.28 ± 2.84	5.57 ± 3.24	0.66
Total biopterin, nmol/L, mean ± SD	14.24 ± 4.34	14.82 ± 4.96	0.56	12.16 ± 3.03	12.97 ± 4.14	0.30
Homovanillic acid, nmol/L, median (range)	63.7 (32.8-170.0)	80.6 (40.7-267.1)	0.006	89.2 (29.6-229.5)	163.0 (40.0-891.4)	<0.001
Glutamic acid, µmol/L, median (range)	46.00 (20-120)	47.00 (12-108)	0.88	36.00 (17-82)	37.50 (17-78)	0.36
Serine, µmol/L, mean ± SD	91.00 ± 19.28	85.17 ± 21.98	0.12	94.04 ± 22.20	79.65 ± 23.97	0.002
Glycine, µmol/L, median (range)	183.00 (118-445)	196.00 (111-365)	0.83	201.50 (119-314)	191.96 (110-335)	0.25
Citrulline, µmol/L, mean ± SD	39.12 ± 11.14	44.84 ± 13.33	0.01	23.22 ± 6.14	24.66 ± 9.96	0.34
Arginine, µmol/L, mean ± SD	63.70 ± 15.16	64.39 ± 16.77	0.81	52.61 ± 18.73	48.41 ± 21.34	0.25
Taurine, µmol/L, mean ± SD	45.04 ± 12.56	47.49 ± 12.20	0.28	35.24 ± 10.97	37.36 ± 20.10	0.47
Methionine, µmol/L, mean ± SD	21.48 ± 4.82	20.86 ± 4.84	0.48	35.89 ± 11.31	30.26 ± 10.68	0.008
Tryptophan, µmol/L, mean ± SD	39.31 ± 8.98	38.28 ± 8.28	0.51	41.05 ± 9.95	35.02 ± 10.91	0.003
Tyrosine, µmol/L, median (range)	62.00 (37-161)	63.00 (37-118)	> 0.99	72.50 (41-142)	66.00 (40-141)	0.13
Phenylalanine, µmol/L, mean ± SD	56.94 ± 8.30	59.93 ± 10.21	0.08	82.33 ± 13.70	80.02 ± 13.86	0.36
Isoleucine, µmol/L, mean ± SD	64.73 ± 14.76	60.07 ± 18.45	0.12	75.74 ± 17.79	71.61 ± 21.57	0.25
Leucine, µmol/L, mean ± SD	122.37 ± 31.49	113.28 ± 32.79	0.12	142.94 ± 30.37	132.83 ± 38.36	0.11
Valine, µmol/L, mean ± SD	236.55 ± 38.69	229.54 ± 56.99	0.42	226.01 ± 41.64	213.78 ± 53.61	0.16
BCAA, µmol/L, mean ± SD	423.66 ± 80.58	402.89 ± 104.77	0.21	444.70 ± 86.34	418.21 ± 111.13	0.15
Tryptophan / LNAA ratio, mean ± SD	7.24 ± 1.28	7.39 ± 1.45	0.53	6.85 ± 1.39	6.15 ± 1.37	0.009
Tyrosine / LNAA ratio, mean ± SD	12.67 ± 2.87	13.31 ± 3.51	0.27	13.46 ± 2.81	13.37 ± 3.12	0.86
Phenylalanine / LNAA ratio, mean ± SD	10.92 ± 1.46	12.25 ± 2.74	0.002	14.81 ± 1.70	15.74 ± 2.74	0.03
Phenylalanine / tyrosine ratio, mean ± SD	0.91 ± 0.18	0.95 ± 0.19	0.14	1.12 ± 0.19	1.19 ± 0.22	0.09
Citrulline / arginine ratio, mean ± SD	0.65 ± 0.24	0.72 ± 0.22	0.07	0.49 ± 0.22	0.59 ± 0.29	0.05
TSM ratio, mean ± SD	2.56 ± 1.20	3.04 ± 1.46	0.05	1.24 ± 0.69	1.88 ± 1.28	0.003

BCAA = Branched Chain Amino Acids (Isoleucine + Leucine + Valine); LNAA: other Large Neutral Amino Acids; TSM ratio = (Taurine / Serine x Methionine) x 100.

In the univariate logistic regression analysis (Table 2), the postoperative levels of neopterin (P < 0.001), HVA levels (P < 0.001), and the ratios of phenylalanine to LNAA (P = 0.03) and TMS (P = 0.003) were significantly higher in participants with delirium than in those without. The ratio of tryptophan to LNAA was significantly lower in participants with delirium (P = 0.009), as were methionine (P = 0.008), serine (P = 0.002), and tryptophan (P = 0.003). Similar to the preoperative data, the postoperative ratio of tyrosine to LNAA and BH4 levels did not differ significantly between the groups.

Table 3. Multiple logistic regression models of delirium after cardiac surgery

Measurement	Beta (S.E.)	Odds Ratio	(95% CI)	*P*-value
Pre-operative measures [1]				
Neopterin [2]	0.047 (0.018)	1.05	(1.01-1.08)	0.009
MMSE score < 28	1.479 (0.454)	4.39	(1.80-10.69)	0.001
EuroSCORE > 6	1.043 (0.492)	2.84	(1.08-7.45)	0.03
Surgery type [3]				0.02
Valve	-0.309 (0.534)	0.73	(0.26-2.09)	0.56
CABG and Valve	1.463 (0.596)	4.32	(1.34-13.89)	0.01
Constant	-1.376 (0.432)	0.25		0.001
Post-operative measures [4]				
Neopterin > 44 nmol/L	1.345 (0.572)	3.84	(1.25-11.77)	0.02
HVA [2]	0.009 (0.004)	1.01	(1.00-1.02)	0.04
MMSE score < 28	1.199 (0.449)	3.32	(1.38-7.99)	0.008
Constant	-2.231 (0.536)	0.11		< 0.001

S.E. = Standard Error; 95% CI = 95% Confidence Interval; CABG = coronary artery bypass graft; MMSE: Mini Mental State Examination.

[1] Model chi-square: 39.800, degrees of freedom *(df)* 5, P < 0.001. Hosmer & Lemeshow goodness of fit test 6.431, *df* 7, P = 0.49. Nagelkerke R^2 = 0.364; area under the receiver operating characteristic curve (AUC) 0.815, 95% CI = 0.741-0.890, P < 0.001.

[2] Grand mean centred continuous variable (odds value increases with every 1 nmol/L added to the variable).

[3] Surgery Type, reference group CABG (Coronary Artery Bypass Graft surgery)

[4] Model chi-square: 41.876, *df* 3, P <0.001. Hosmer & Lemeshow goodness of fit test: 8.625, *df* 8, P = 0.375. Nagelkerke R^2 = 0.399. AUC: 0.820, 95% C I= 0.744-0.896, P < 0.001.

Because the association between postoperative neopterin levels and delirium was nonlinear in the logistical regression analysis, a dichotomisation with a cut-off value of 44 nmol/L was performed. The final postoperative multiple logistic regression model (Table 3) included neopterin and HVA levels and preoperative cognitive functioning as measured using the MMSE. Neopterin levels greater than 44 nmol/L were found to be associated with a 3.8 times greater risk of delirium, and higher HVA levels were associated with an 1.01 times greater risk of delirium. In this postoperative model, a preoperative MMSE score less than

28 was associated with a 3.3 times higher postoperative delirium risk. The overall fit of the postoperative model was adequate (model chi-square 41.876, *df* 3, $P < 0.001$; Hosmer & Lemeshow goodness of fit test 8.625, *df* 8, $P = 0.37$; Nagelkerke $R^2 = 0.399$ and ROC curve 0.820, 95% CI 0.744-0.896, $P < 0.001$).

DISCUSSION

This study examined pterins and amino acids for their possible role as biomarkers to predict the occurrence of delirium after cardiac surgery. The results show that individuals with a high preoperative neopterin level have greater risk for delirium after surgery, after controlling for well-known risk factors for delirium (greater cognitive dysfunction and co-morbidity) and possible confounding variables (CRP, creatinine, urea and type of surgery). This suggests that, even before surgery, there is greater cellular immune activation in individuals at risk of delirium after cardiac surgery. This is in agreement with the higher neopterin levels found to be associated with the extent and activity of atherosclerosis, with the number of affected coronary arteries, and with cerebral ischemia [8]. However, atherosclerosis and cerebral ischemia-related items in the EuroSCORE, such as extra-cardiac arteriopathy and neurological dysfunction affecting ambulation or daily functioning (only one participant in the group without delirium) did not differ significantly between the participants with and without delirium. The fact that plasma neopterin levels, MMSE scores and EuroSCORE values all remained in the multifactor model and had medium or small correlations suggests that they represent different aspects of these processes. An alternative explanation for the higher plasma neopterin levels could be impaired renal excretion in the participants with delirium, [8] although neopterin level was significantly associated with delirium even when controlling for renal functioning.

The high plasma neopterin levels in participants who developed delirium also indicate high oxidative stress, a finding consistent with the high preoperative levels of citrulline and high ratio of citrulline to arginine in the participants with delirium, although in multiple logistic regression analysis, these associations did not affect the association of neopterin and delirium.

No significant relationship was found between pre- or postoperative plasma levels of BH_4 and delirium, suggesting that this essential cofactor in the synthesis of catecholamines and serotonin was functioning within normal ranges or that plasma BH_4 is a poor indicator of cerebral BH_4. There were significant differences between the two groups in factors related to serotonin metabolism in the brain (e.g., the ratio of plasma tryptophan to LNAA) only after surgery. This is in agreement with a previous study in the same participant population [16] (although of younger age) and a recent study on risk factors for delirium in critically ill individuals [30]. The current study also confirmed that the ratio of phenylalanine to LNAA before surgery was significantly higher in participants with delirium than in those without and that this difference increased further after surgery, as was observed previously, [16] although in the multiple regression analysis, this factor did not contribute to the model and was, therefore, excluded. An alternative explanation of the preoperatively high phenylalanine levels in participants with delirium could have been high sympathetic activation for cardiac reasons, but no differences were found between participants with and without delirium in prevalence of cardiac disorders that are responsible for sympathetic activation.

Individuals with delirium may have low serotonergic transmission after cardiac surgery because of a particular affinity of phenylalanine to the binding site on the transporter of the blood-brain barrier in preference to the other LNAAs, including tryptophan. In this way, high plasma concentrations of phenylalanine, as reflected in this ratio, may impair the uptake of the other LNAAs, such as tryptophan [18]. Alternatively, phenylalanine may inhibit the monoamine synthesizing enzymes interfering with the synthesis of serotonin, dopamine and norepinephrine [31].

In agreement with other studies, in the current study's population, the factors associated with frailty (e.g., age, cognitive functioning, cardiac risk factors and co-morbidity) were associated with the risk of delirium [32,33]. The high TSM ratio found in participants with delirium in the univariate analyses is thought to be related to catabolism, which is considered to be part of the frailty concept [34].

Study limitations and strengths

Because the present study was conducted in a specific group of older adults undergoing elective cardiac surgery, the results may not be generalizable to other populations of individuals with delirium. The definition of clinically relevant delirium, as used in this protocol, was based on a compromise between the epidemiological findings that even delirium of short duration is associated with adverse outcomes and the study requirement that delirium should be associated with marked alterations of the underlying biochemical pathways. Although expert opinions were used to formulate the definition of clinically relevant delirium, this choice remains somewhat arbitrary. To assess the effect of the delirium definition used on the models, the data were reanalysed with shorter and longer durations of delirium (e.g., ≥1 days, ≥3 days). This approach did not change the results. Furthermore, the presence of delirium was assessed using the CAM-ICU. Although this indicates a 24-hour reporting period, the CAM-ICU may not completely capture the fluctuating clinical manifestations of delirium. Finally, because the analyses were limited to pre- and postoperative pterins and amino acid levels, only the known predictors of delirium were taken into account. Other factors that may influence the development of delirium (e.g., operative and genetic factors) were beyond the scope of this study.

The strengths of the study include the large group of older adults participating in this prospective study. Also, the use of pre-, and postoperative assessments and extensive daily assessments after surgery (during the hospitalization) allowed for careful monitoring and measurement of the ongoing processes. Furthermore, sometimes unstable chemical compounds (e.g., BH_4) were measured using the most-accurate validated methods available [26]. Finally, to the knowledge of the authors, this is the first study to examine the relationship between neopterin levels in plasma and the occurrence of postoperative delirium in individuals undergoing cardiac surgery.

CONCLUSION

In older adults, plasma neopterin levels before cardiac surgery were associated with occurrence of postoperative delirium. Although neopterin is regarded as a marker of macrophage or immune activation, the pathway by which neopterin is associated with delirium remains to be elucidated. Higher preoperative plasma levels of neopterin, a lower cognition score (on the MMSE), and higher cardiac risk factors (EuroSCORE) before surgery, as well as undergoing combined CABG and valve surgery, increased the risk of delirium. Postoperative neopterin and HVA levels and preoperative functioning as measured with the MMSE were associated with delirium after cardiac surgery. Neopterin may be a candidate biomarker for delirium after cardiac surgery in older adults. Confirmation of the possible role of plasma neopterin as a biomarker for delirium in cardiac surgery in other populations of different ages or with other etiological factors for delirium is recommended. More research on the pathogenetic pathways involving neopterin and its association with delirium is needed.

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Chapter

6

Postoperative delirium in the long-term diminishes attention and executive functioning without affecting memory

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Chapter

7

General discussion and Conclusions

Chapter

8

Summary

Delirium is the most frequently occurring neuropsychiatric disorder in a general hospital, with incidences ranging from 5 to 32%. But in older patients (aged 60 or older) undergoing cardiac surgery the incidence is described to range from 20 to 52%. Because of its relation with serious adverse outcome, such as increased morbidity, medical complications and mortality, delirium comprises an important clinical problem.

Predictors of delirium

In order to find ways to prevent delirium or enhance early detection, preoperative and operative predictors of delirium after cardiac surgery in older patients were examined in **Chapter 2**. In a prospective cohort study, 201 patients aged 70 years and older who underwent cardiac surgery were assessed daily, using the Confusion Assessment Method-Intensive Care Unit (CAM-ICU), to establish whether they developed a delirium or not. Sixty-three patients (31,3 %) developed a delirium. Before surgery patients with delirium showed significantly lower Mini-Mental State Examination (MMSE) scores, higher creatinine levels, and during surgery the extracorporeal circulation (ECC) time was significantly longer than in patients without delirium. In patients with delirium after cardiac surgery the 30-day mortality was substantially higher (14% vs. 0 %) than in patients who did not experience a delirium. Patients with an increased risk for delirium should, therefore, be candidates for preventive interventions, such as discontinuation of potentially nephrotoxic drugs, performing an extensive geriatric check-up before surgery and prophylactic use of haloperidol, aiming at improving overall surgical outcomes.

Wrist-Actigraphy and delirium

Patients with delirium frequently show disturbed circadian motor activity patterns, but objective and quantitative data are scarce. In **Chapter 3,** wrist-actigraphy was evaluated as a method to quantify 24-hr motor activity patterns, during 5-sequential days after elective cardiac surgery in 79 patients, aged 65 years or older, who experienced a short delirium (2-3 days), a sustained delirium (≥ 4 days) or did not develop a clinically relevant delirium. Delirium assessments were carried out daily with the CAM-ICU and the Delirium Rating Scale-Revised 98 (DRS-R98). The activity amplitude, daytime activity/minute and daytime restlessness index were significantly higher, and the daytime immobility minutes were significantly lower in patients without delirium or with a short delirium, when compared to patients with a sustained delirium. Wrist-actigraphy proves a valuable method to quantify motor activity patterns in relation to the clinical state in older patients with a delirium after cardiac surgery.

Delirium is poorly recognised in clinical situations, especially the hypoactive subtype. In **Chapter 4** the use of wrist-actigraphy, as a tool to objectively quantify 24-hour motor activity patterns, was explored in 88 patients after cardiac surgery, aged 65 years or older, in order to improve early recognition of delirium. Based on daily assessments, using the CAM-ICU, 70 patients could be analysed, of which 38 were delirious and 32 were non-delirious on the first day after surgery. Delirious patients displayed lower mean activity levels during the first night after surgery, lower restlessness during the first day and lower mean activity of the 5 hours with the lowest motor activity within 24-hours, when compared to patients without a delirium. As early as in the first night and day after cardiac surgery, differences in motor activity could be demonstrated between patients with and without a delirium. Wrist-actigraphy has the potential to be a screening method that could lead to improved early recognition and treatment of delirium.

Pterines and Amino Acids before and during delirium

Immune activation, oxidative stress and cerebral neurotransmitter disturbances have all been implicated in the pathophysiology of delirium. The pterins, i.e.: neopterin and tetrahydrobiopterin, are presumed to play a role in metabolic processes associated with delirium. Neopterin is regarded as a marker of cellular immune activation and oxidative stress. It originates from monocytes and macrophages, which are activated by various insults, such as tissue damage, inflammation and hypoxia. Tetrahydrobiopterin is the essential co-factor in the synthesis of the neurotransmitters dopamine, norepinephrine, serotonin and in the formation of certain amino acids. In **Chapter 5** the associations between plasma levels of pterins, amino acids and delirium were examined in 125 patients undergoing cardiac surgery. Plasma pterins and amino acids were measured before and after cardiac surgery and analysed in relation to age, sex, medical co-morbidity, general cognitive functioning (MMSE-score), and cardiac risk factors (European System for Cardiac Operative Risk Evaluation score, EuroSCORE), using multiple logistic regression analyses. Delirium was associated with the preoperative measurements of plasma levels of neopterin, MMSE-score of 27 and less, EuroSCORE score above 6, and combined coronary artery bypass graft and valve surgery. The postoperative measures associated with delirium were plasma neopterin level above 44 nmol/L, higher levels of homovanillic acid (HVA), and preoperative MMSE-score of 27 and lower. High preoperative plasma neopterin levels predicted delirium after cardiac surgery in older patients, in addition to the well-known risk factors poor cognitive function, high cardiac-surgical risk and combined CABG and valve surgery. Plasma neopterin may be a candidate biomarker for delirium after cardiac surgery in older patients.

Cognitive functioning and delirium

Delirium has been associated with diminished cognitive functioning, but it is unclear whether cognitive dysfunction is pre-existing, caused by delirium itself, the somatic condition or the medical intervention. Moreover, different cognitive domains have only sparsely been studied. In **Chapter 6** the association between delirium and cognitive functioning in different

domains before and long-term after cardiac surgery was studied in 201 patients, aged 70 or older, of which 163 could be analysed. The drop out due to mortality in the time till the planned neuropsychological retesting was substantially higher in patients with delirium than in those without delirium (21% vs. 4%). The cognitive functions were assessed before and, on average, 8,5 months after surgery, using the Trail Making Test A and B (TMTA, TMTB) for attention and combined attention and executive functioning respectively, the Stroop Color-Word Test (Stroop Interference) for executive functioning, the Rey Auditory-Verbal Learning Test (RAVLT) and the Digit Span backwards for memory functions, the Digit Symbol-Coding for processing speed, the Grooved Pegboard Test for motor speed and MMSE for global cognitive functioning. Delirium was assessed using the CAM-ICU every day after cardiac surgery. In the long-term after cardiac surgery delirium was significantly associated with diminished attention and diminished executive functioning, but not with delayed memory, working memory and processing speed.
This emphasizes the relevance of delirium prevention, but does not support the notion that having experienced a delirium in the long-term leads to sustained memory decline or Alzheimer's or vascular dementia.

In **Chapter 7** the main findings of our research, as previously summarized, are presented, the clinical implications are discussed and conclusions are drawn.

Chapter

9

Nederlandse Samenvatting

Delirium is de meest voorkomende neuropsychiatrische stoornis in het algemene ziekenhuis, met een incidentie variërend van 5 tot 32%. Bij oudere patiënten (van 60 jaar of ouder) die een hartoperatie ondergaan worden hogere incidenties beschreven van 20 tot 52%. Omdat het optreden van een delirium samenhangt met verscheidene negatieve uitkomstmaten, zoals toegenomen medische complicaties, morbiditeit en mortaliteit, vormt het een belangrijk klinisch probleem.

In dit proefschrift zijn de resultaten beschreven van onderzoek naar het delirium bij oudere patiënten die een hartoperatie hebben ondergaan, waarbij verschillende invalshoeken zijn belicht. Allereerst werden de voorspellende factoren voor een delirium onderzocht. Ten tweede werd het gebruik van een nieuwe methode om bewegingspatronen te meten door middel van pols-actigrafie tijdens een delirium onderzocht op bruikbaarheid en werd het gebruik van deze methode voor vroege detectie van een delirium onderzocht. Ten derde werd onderzoek gedaan naar de rol van pterines en aminozuren bij het delirium en tenslotte werd het cognitief functioneren in relatie tot het optreden van een delirium onderzocht.

Voorspellende factoren voor een delirium

Om antwoord te krijgen op de vraag hoe een delirium mogelijk is te voorkómen of vroege detectie ervan is te verbeteren, werden (peri)operatieve voorspellende factoren voor een delirium na een hartoperatie onderzocht (**Hoofdstuk 2**). In een prospectief cohort onderzoek werden 201 patiënten, van 70 jaar of ouder, die een hartoperatie ondergingen, na de operatie dagelijks onderzocht op de ontwikkeling van een delirium. Het optreden van een delirium werd vastgesteld met behulp van de 'Confusion Assessment Method-Intensive Care Unit' (CAM-ICU), een meetinstrument waarmee de criteria voor een delirium conform de 'Diagnostics and Statistics manual of Mental disorders, 4th edition, Text Revision' (DSM-4-TR, classificatie-systeem van psychiatrische stoornissen) worden onderzocht. Drieënzestig patiënten (31,3%) ontwikkelden een delirium. Vóór de hartoperatie toonden de patiënten die een postoperatief delirium ontwikkelden significant lagere Mini-Mental State examination-scores (MMSE), hetgeen op een slechtere globale cognitie wijst en hogere plasma creatinine concentraties, dus een verminderde nierfunctie, ten opzichte van de patiënten die geen delirium ontwikkelden. Daarnaast was tijdens de hartoperatie de extracorporele circulatietijd (ECC-tijd), de tijd waarin de hartlongmachine de circulatie en oxygenatie van het bloed overneemt, significant verlengd bij de patiënten die een delirium ontwikkelden. De ECC-tijd wordt beschouwd als een maat voor de complexiteit van de hartoperatie, hetgeen betekent dat postoperatief delirante patiënten meer complexe hartoperaties hadden. Ook de 30-dagensterfte was aanzienlijk hoger (14% t.o.v. 0%) bij delirante patiënten dan bij degenen die geen delirium doormaakten. Patiënten met een verhoogd risico op een delirium zouden gelet op deze resultaten, in aanmerking moeten komen voor preventieve interventies. Te denken valt aan het staken van potentieel nefrotoxische medicatie, algemeen geriatrisch onderzoek en optimalisatie van de preoperatieve klinische conditie, naast mogelijk het profylactische gebruik van haloperidol, met de bedoeling de algehele resultaten van de hartoperaties bij ouderen te verbeteren.

Pols-actigrafie en delirium

Pols-actigrafie is een methode om met behulp van een bewegingssensor (met het formaat van een polshorloge) die aan de pols wordt bevestigd, objectieve en kwantitatieve data van de motorische activiteit per tijdseenheid te verzamelen. Bij verschillende ziekten, onder andere neuropsychiatische aandoeningen zoals de ziekte van Alzheimer, de ziekte van Parkinson en depressie, is pols-actigrafie reeds gebruikt om inzicht te krijgen in de motorische activiteit en het 24-uurs bewegingspatroon. Delirante patiënten vertonen vaak motorische onrust, apathie en stoornissen in het circadiane motorische activiteitenpatroon. Bovendien zijn de deliriumsubtypen op basis van de motorische symptomen gekarakteriseerd. Desondanks zijn er weinig objectieve en kwantitatieve data hierover bekend. In **Hoofdstuk 3** werd pols-actigrafie gebruikt als methode om 24-uurs motorische activiteitenpatronen te kwantificeren gedurende 5 opeenvolgende dagen bij 79 patiënten van 65 jaar of ouder die een kortdurend, langdurend of geen delirium doormaakten. Dagelijks werd de aanwezigheid van een delirium vastgesteld met behulp van de CAM-ICU en de Delirium Rating Scale-Revised 98 (DRS-R98). Een kortdurend delirium was gedefinieerd als een delirium volgens de CAM-ICU dat 2 of 3 dagen duurde. Van een langdurend delirium was sprake als het 4 of meer dagen duurde. De amplitude van de activiteit, de gemiddelde activiteit per minuut overdag en de fragmentatie-index overdag waren significant hoger bij patiënten zonder klinisch relevant delirium en met een kortdurend delirium, in vergelijking met patiënten met een langdurend delirium. Het aantal minuten immobiliteit overdag was significant hoger bij de groep patiënten die langdurend delirant was. Pols-actigrafie blijkt een betrouwbare en valide methode te zijn om motorische activiteitenpatronen te kwantificeren. Door deze activiteitenpatronen te relateren aan klinische en biologische kenmerken van oudere delirante patiënten kan de samenhang worden nagegaan tussen deze activiteitenpatronen enerzijds en zowel (vroeg-)detectie en subtypen van delirium als mogelijke onderliggende pathogenetische mechanismen anderzijds.

In klinische situaties blijkt een delirium slecht te worden herkend, in het bijzonder wanneer het een hypokinetisch delirium betreft. In **Hoofdstuk 4** werd het gebruik van pols-actigrafie onderzocht als hulpmiddel om de vroege detectie van het delirium te verbeteren in een groep van 88 patiënten van 65 jaar oud of ouder die een hartoperatie ondergingen. Gebaseerd op de resultaten van de CAM-ICU, die dagelijks werd afgenomen, konden 70 patiënten worden geanalyseerd van wie er 38 delirant en 32 niet delirant werden op de eerste dag na de operatie. De delirante patiënten vertoonden een lagere gemiddelde motorische activiteit gedurende de eerste nacht na de operatie, een lagere fragmentatie-index gedurende de eerste dag na de operatie en een lagere gemiddelde activiteit in de 5 uren met de laagste motorische activiteit binnen 24-uur, in vergelijking met de patiënten zonder delirium. Al in de eerste nacht na een hartoperatie konden met pols-actigrafie, op objectieve wijze, verschillen in motorische activiteit worden aangetoond tussen patiënten met of zonder delirium. Pols-actigrafie zou in potentie bruikbaar kunnen zijn als detectiemethode om de vroege herkenning en behandeling van delirium te verbeteren.

Pterines en aminozuren vóór en tijdens een delirium

In de pathofysiologie van het delirium kunnen zowel immuunactivatie als oxidatieve stress en ontregeling van de cerebrale neurotransmissie een rol spelen. Ook is het optreden van een delirium mogelijk geassocieerd met metabole processen waarin de pterines, in het bijzonder neopterine en tetrahydrobiopterine, een rol spelen. Neopterine wordt beschouwd als een maat voor de cellulaire immuunactivatie en oxidatieve stress. Geactiveerde monocyten en macrofagen produceren neopterine naar aanleiding van diverse schadelijke factoren, waaronder weefselschade, ontsteking en hypoxie. Tetrahydrobiopterine is de essentiële cofactor in de synthese van de neurotransmitters dopamine, noradrenaline en serotonine en bij de vorming van enkele aminozuren. In **Hoofdstuk 5** wordt onderzoek beschreven naar de associatie tussen een delirium en de plasmaconcentraties van pterines en aminozuren bij 125 patiënten die een hartoperatie ondergingen, in relatie tot leeftijd, geslacht, medische comorbiditeit, globaal cognitief functioneren (MMSE-score) en cardiale risicofactoren (European System for Cardiac Operative Risk Evaluation score, EuroSCORE). Het optreden van een delirium bleek geassocieerd te zijn met de preoperatieve plasmaconcentratie van neopterine, een MMSE-score van 27 of lager, een EuroSCORE-score boven 6 en gecombineerde kransslagader- (CABG, coronary artery bypass graft) en hartklepchirurgie. Postoperatief bleken plasmaconcentraties van neopterine boven 44 nmol/l, hogere concentraties van homovanillinezuur en de preoperatieve MMSE-score van 27 en lager samen te hangen met het optreden van een delirium. Hogere preoperatieve plasmaconcentraties van neopterine voorspelden het optreden van een delirium bij oudere patiënten na een hartoperatie, naast de bekende risicofactoren, zoals slechtere cognitieve functie, verhoogd hartchirurgisch risico, en gecombineerde CABG- en hartklepchirurgie. De plasmaconcentratie van neopterine kan beschouwd worden als een kandidaat biomarker voor een delirium na hartchirurgie bij oudere patiënten.

Cognitief functioneren en delirium

Het delirium is geassocieerd met verminderd cognitief functioneren. Het is in het algemeen echter onduidelijk of het cognitieve disfunctioneren al voor de hartchirurgie en het delirium aanwezig is, dan wel door het delirium zelf óf door de onderliggende somatische conditie of medische interventie veroorzaakt wordt. Bovendien zijn de verschillende cognitieve domeinen in studies naar de cognitieve effecten van een delirium slechts zeer beperkt onderzocht. In **Hoofdstuk 6** werd de associatie onderzocht tussen het optreden van een delirium en het cognitief functioneren op verschillende neuropsychologische domeinen, vóór een hartoperatie en op de lange termijn na een hartoperatie, bij 201 patiënten van 70 jaar en ouder. Uiteindelijk konden de resultaten van 163 patiënten worden geanalyseerd. De uitval door overlijden in de periode tussen de hartoperatie en de neuropsychologische hertest was substantieel hoger bij delirante dan bij niet-delirante patiënten (21% versus 4%). De cognitieve functies werden op de dag vóór de hartoperatie en gemiddeld 8,5 maanden na de operatie gemeten met behulp van de Trail-Making Test A en B voor aandacht en gecombineerd aandacht en executief functioneren, met de Stroop-Color-Word Test (Stroop Interference) voor executief functioneren, de Rey Auditory-Verbal Learning Test en de Digit Span backwards voor de geheugenfuncties, de Digit Symbol-Coding voor de snelheid van het werkgeheugen, de Grooved Pegboard Test voor snelheid van het motorisch functioneren en de MMSE voor het globaal cognitief functioneren. Op de lange termijn na een hartoperatie was een delirium significant geassocieerd met verminderde aandacht en verminderd executief functioneren, maar niet met stoornissen van het geheugen, het functioneren en de snelheid van het werkgeheugen of de snelheid van het motorisch functioneren. Deze resultaten benadrukken het belang van deliriumpreventie, maar weerspreken de veronderstelling dat het doormaken van een delirium op de lange termijn leidt tot blijvende geheugenstoornissen of dementie.

In **Hoofdstuk 7** worden de belangrijkste bevindingen van ons onderzoek, zoals verkort weergegeven in de bovenstaande samenvatting, gepresenteerd en worden de klinische implicaties van het onderzoek bediscussieerd en conclusies getrokken. De conclusies luiden:

- Hogere preoperatieve plasma creatinine spiegels, lagere MMSE-scores en een langere duur van de extracorporele circulatie zijn geassocieerd met een verhoogd risico op delirium na hartchirurgie bij oudere patiënten.
- Pols-actigrafie is een praktische en bruikbare methode om op objectieve wijze circadiane motorische patronen te meten bij patiënten met en zonder delirium. Al in de eerste nacht na een hartoperatie kan het gebruikt worden om patiënten met en zonder delirium van elkaar te onderscheiden, zelfs als delirant gedrag nog nauwelijks als zodanig te herkennen is.
- Plasma neopterine concentraties, die de mate van cellulaire immuunactivatie en oxidatieve stress reflecteren, zijn hoger vóór de hartoperatie bij patiënten die een delirium ontwikkelden ten opzichte van hen die geen delirium ontwikkelden. Na een hartoperatie zijn hogere concentraties van neopterine, homovanillinezuur (HVA) en verhoogde ratio's van fenylalanine (Phe) ten opzichte van de andere grote neutrale aminozuren (LNAA, de Phe-LNAA ratio) geassocieerd met een delirium. Hetgeen wijst op

verhoogde dopaminerge neurotransmissie tijdens een delirium. Bovendien suggereren de verhoogde Phe-LNAA ratio en verlaagde tryptofaan ten opzichte van de LNAA ratio een verlaagde serotonerge neurotransmissie tijdens een delirium na hartoperatie.

- Een delirium is op de lange termijn geassocieerd met verminderde aandachts- en executieve functies, maar niet met stoornissen in de geheugenfuncties of met vertraging van het werkgeheugen of de motorische functies. Het gegeven dat de verschillende cognitieve domeinen in verschillende richtingen worden beïnvloed op de lange termijn na een delirium, pleit tegen het gebruik van meetinstrumenten waarin een sommatie van scores van verschillende cognitieve domeinen worden gebruikt, zoals de MMSE. Het effect van een delirium op de cognitieve functies, wordt dus met het klinisch meest gebruikte meetinstrument, de MMSE, niet goed gemeten.

Addendum

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List of abbreviations
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LIST OF ABBREVIATIONS

5-HIAA	5-Hydroxyindoleacetic acid
5-HT	5-Hydroxytriptamine or Serotonin
ANOVA	Analysis of variance (statistical procedure)
AoX	Aorta cross clamp (time, in minutes)
APA	American Psychiatric Association
AVR	Aortic valve replacement
BCAA	Branched chain amino acids (Isoleucine + Leucine + Valine)
BH4	Tetrahydrobiopterin
BMI	Body mass index
CABG	Coronary Artery Bypass Graft
CAM-ICU	Confusion Assessment Method-Intensive Care Unit
CCI	Charlson Comorbidity Index
CI	Confidence interval
CRP	C-reactive protein
df	Degrees of freedom
Digit Span	Digit Span backwards, number of correct trails
Digit Symbol	Digit Symbol-coding, number of correct symbols
DMC	Delirium Motor Checklist
DMSS	Delirium Motor Subtype Scale
DRS-R98	Delirium Rating Scale- Revised version '98
DSM	Diagnostics and Statistical manual of Mental disorders (-edition number)
ECC	Extracorporeal circulation (time, in minutes)
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalogram
EuroSCORE	European System for Cardiac Operative Risk Evaluation
Gr Pegboard	Grooved Pegboard Test (seconds)
GTP	Guanosine triphosphate
GTPCH	Guanosine triphosphate cyclohydrolase
HADS	Hospital Anxiety and Depression Scale
HPLC	High-performance liquid chromatography
HVA	Homovanillic acid
IABP	Intra aortic balloon pump
ICU	Intensive care unit
IQR	Inter quartile range
L5	Mean activity of the 5 h with the least activity within a 24-h period
L-DOPA	3,4-Dihydro-L-phenylalanine

LNAA	Large neutral amino acids
M10	Mean activity of the 10 h with the highest activity within a 24-h period
MMSE	Mini Mental State Examination
MVP	Mitral valve annuloplasty
MVR	Mitral valve replacement
NO	Nitric oxide
Non-cr-Del	Non-clinically relevant delirium group
OR	Odds ratio
Phe	Phenylalanine
RAVLT	Rey Auditory-Verbal Learning Test
RAVLT-delay	Number of correctly remembered words after 20 minutes delay in RAVLT.
RAVLT-total	Total number of good responses in 5 sessions in RAVLT
ROC	Receiver-operating characteristic (curve)
ROS	Reactive oxygen species
SD	Standard deviation
SE	Standard Error
Short-Del	Short duration of delirium group (2-3 days delirious)
Stroop If	Stoop Color-Word Test interference score
Sustained-Del	Sustained duration of delirium group (4 or more days delirious)
TMT	Trail Making Test (-A: part A, -B: past B)
TSM ratio	(Taurine / Serine x Methionine) x 100 ratio
TVP	Tricuspid valve annuloplasty
TVR	Tricuspid valve replacement
Valve	Surgery on aortic, mitral or tricuspid valve
WAIS-III	Wechsler Adult Intelligence Scale-III

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Robert Jan Osse

CURRICULUM VITAE

Robert Jan Osse was born on December 5th 1963 in Leiden, the Netherlands.

From 1982 to 1989 he studied Medicine at the Erasmus University in Rotterdam, while working as teaching-assistant and research-assistant at the Departments of Anatomy and Neuroanatomy. He received his masters' degree (doctoraal) in 1987. After graduating for his medical degree in 1989, he worked as a psychiatry resident at Bavo Psychiatric Center, Noordwijkerhout, and at RIAGG 's-Hertogenbosch and Delta Psychiatric Center, Hellevoetsluis.

From 1994 to 1998 he received his training as psychiatrist at Delta Psychiatric Center, Rotterdam / Poortugaal, under supervision of Dr. L. Timmerman, psychiatrist. He followed supplementary training in consultation-liaison psychiatry at Dijkzigt, Academic Hospital Rotterdam, under supervision of A.M. van Hulst, psychiatrist. On October 1st 1998, he was registered as a psychiatrist and psychotherapist.

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Robert Jan is married to Anke Griffioen, they have two children Hester and Inne.