DELIRIUM AFTER CARDIAC SURGERY

a prospective study

Delirium na een hartoperatie
een prospectieve studie

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit te Rotterdam
op gezag van de Rector Magnificus

Prof.Dr. P.W.C. Akkermans, M.A.

en volgens besluit van het college voor promoties.
De openbare verdediging zal plaatsvinden op
woensdag 2 november 1994 om 13.45 uur.

door
ROSA CORNELIA VAN DER MAST
geboren te Medan

DELIRIUM AFTER CARDIAC SURGERY

a prospective study

Promotores:	Prof.Dr. L. Pepplinkhuizen
	Prof.Dr. W.J. Schudel
Overige leden:	Prof.Dr. J.D.F. Habbema
	Prof.Dr. E.P. Krenning

From the Department of Psychiatry
Erasmus University Rotterdam
and University Hospital Rotterdam - Dijkzigt
Dr. Molewaterplein 40
3015 GD Rotterdam
The Netherlands

This study was carried out at the Department of Psychiatry (Prof.Dr. W.J. Schudel) and the Thoraxcenter (Prof.Dr. E. Bos) of the University Hospital Rotterdam - Dijkzigt and the Center for Clinical Decision Science, Department of Mental Health (Prof.Dr. J.D.F. Habbema) of the Erasmus University Rotterdam, The Netherlands. It was supported by the Departments of Psychiatry, Thoracic Surgery, Nuclear Medicine and Clinical Chemistry of the University Hospital Rotterdam and by Duphar-Nederland b.v., SmithKline Beecham Farma b.v. and Eli Lilly.

De publicatie van dit proefschrift werd mede mogelijk gemaakt door Duphar Nederland b.v.

Omslagontwerp: Els Dekker, Amsterdam
Vormgeving en opmaak: Wendy Collet-de Boer
Benecke Consultants, Amsterdam
Druk: Drukkerij Den Hartog bv, Amsterdam

CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Mast, Rosa Cornelia van der

Delirium after cardiac surgery: a prospective study /
Rosa Cornelia van der Mast. - Amsterdam: Benecke Consultants
Proefschrift Rotterdam. - Met lit. opg. - Met samenvatting in het Engels.
ISBN 90-73637-19-8
Trefw.: delirium.

CONTENTS

Voor wie ik liefheb

Chapter 1

INTRODUCTION

Chapter 1.1

HISTORY

Delirium was one of the first mental disorders described by the ancient medical writers some 2500 years ago [1]. In his extensive and excellent monograph "Delirium: Acute Confusional States", Lipowski describes the historical development of the concept of this disorder in detail, from the time of Hippocrates till the twentieth century [1]. His most important and remarkable finding in tracing the history of delirium is the accuracy and consistency of the clinical description, despite the confusing variety of terms applied over the centuries to the same set of symptoms. Hereafter, the most important facts from his historical outline on delirium will be summarized [1].

At first, in antiquity, what nowadays is called delirium was referred to as 'phrenitis'. It was regarded as an acute mental disorder usually associated with fever and characterized by cognitive and behavioural disturbances as well as disruption of sleep. Phrenitis was described as marked by restless and excited behaviour, while 'lethargus', considered as the opposite of phrenitis, featured listlessness, sleepiness, inertia, memory loss and dulling of the senses. Lethargus could change into phrenitis and vice versa. Only in the late eighteenth century the word delirium gradually came to replace both of the earlier terms. Celsus was the first medical writer known to use the term 'delirium'. He, as the other ancient medical writers, recognized delirium or phrenitis as one of the most important mental disorders at that time.

In the medieval period relatively little was contributed to the concept of delirium and in the twelfth century the interest in mental disorders waned. It was only in the sixteenth century that some interesting developments in the concept of delirium took place. By then, it became recognized that delirium could occur in a wide range of systemic diseases and the importance of thorough medical examination of a delirious patient was emphasized. It was also asserted that a predelirious phase, called 'paraphrenitis' could occur, which might or might not be followed by a full-blown delirium. The prodromal symptoms of phrenitis were insomnia, headache and disturbing dreams. It was stated that the outcome of delirium depended on the constitution of the patient, the nature of the underlying disease and the method of treatment applied. It was noted that disorientation constituted a symptom of delirium and that contrasting states like vigilance and apathy could occur in the same patient on a single day. Other psychopathological features described were abnormalities of imagination (visual hallucinations), reason and memory. In this age, delirium complicating surgery was mentioned for the first time and described as a transient disturbance following fever, pain and excessive bleeding due to wounds, gangrene and operations.

In the seventeenth and eighteenth century the interest in and knowledge of mental disorders increased enormously. Many important contributions appeared such as a treatise on mental disorders by Thomas Willes. He considered delirium not as a disease per se, but rather as a symptom. Like his contemporaries he departed from the traditional humoral theory of delirium, which re-

garded delirium as the result of a disordered secretion of the brain glands.
Frings, in the eighteenth century, explicitly rejected the humoral theory of disease and the treatment of delirium based on it. He criticized the at that time often advocated 'bleeding therapy' and stressed the need for rest and sleep. Even though the essential features of delirium had by now been adequately described, the relevant terminology was still inconsistent and confusing: 'delirium' implied madness or raving, while 'phrenitis' or 'phrensy' referred to delirium associated with febrile and sometimes other somatic diseases. Phrensy was usually divided into primary, that is, due to a disorder of the brain and its membranes, or secondary ('paraphrensy'), that is, resulting from overheating of the brain, due to extracerebral causes. Other interesting contributions in this period included observations on the intriguing relationship between delirium and the disorder of the sleep-wake cycle, the notion that delirium constituted a form of dreaming while the person was awake, the development of the pathogenetic theory that delirium involved 'diminution in the energy of the brain', the classification of delirium among the diseases of sensation, specifically as one with increased sensation and the introduction of the term 'consciousness'. Although it was only in the next century that consciousness came to be regarded as a distinct mental state or function, one whose disturbance ('clouding') was generally regarded as a core abnormality in delirium, the concept now was introduced to denote awareness of one's self, one's body and one's environment. James Sims, in 1799, was the first to use the term 'delirium' in its modern sense to designate a distinct mental disorder rather than to refer to insanity generally, at the same time recognizing the two clinical variants of the syndrome, distinguished by contrasting states of alertness and of psychomotor behaviour.

The works on delirium, appearing in the nineteenth century were mainly written by physicians and surgeons, not by psychiatrists. It was the age of the 'asylum' and of the isolation of psychiatry from the rest of medicine. Since delirium was already considered as an acute and transient complication of a physical illness, it was of no practical importance to the asylum psychiatrist who was only familiar with chronic mental disorders. By now the syndrome of delirium had been clearly delineated and became increasingly recognized as a transient cognitive and behavioural disorder brought about by brain dysfunction, resulting from a wide range of physical (organic) causes. Delirium tremens, thought to be due to intoxication with alcohol or its withdrawal, was described at about the same time. Excellent clinical descriptions were written by different medical authors. Hypoxemia, due to either pulmonary or cardiac disease, and trauma were added to the possible etiological factors for delirium. Dupuytren, a French surgeon, described 'traumatic' delirium, occurring after accidental or surgical trauma and noted the transient nature, the generally good prognosis, the absence of fever and tachycardia and next to other already known features, the insensitivity to pain.
In the second half of the nineteenth century an important development in the concept of delirium took place. From now on it was viewed as a disorder

of consciousness, although some functional mental disorders were also included among diseases featuring altered or clouded consciousness. Initially the terms 'consciousness', 'mind' and 'mentation' were used synonymously, but soon consciousness was accepted as a 'special function of some part or parts of the brain'. It came to be regarded as a product of molecular change in brain tissue, closely related to attention. Another concept, closely connected with delirium and clouding of consciousness, elaborated during this period constituted 'confusion'. It was viewed as a core psychological impairment, characterized by an inability to think coherently and logically, reduced perceptual discrimination and defective memory. Like consciousness it constituted a symptom not only of delirium, but also of some other mental disorders lacking organic aetiology. Because of a tendency to designate the disorders which shared certain clinical features with delirium by many different new terms (such as acute delirium, delirium acutum, amentia, confusional states etc.), a terminological and conceptual chaos was created which hampered a further clarification of the concept of delirium, interfering with the exploration of its aetiology, pathogenesis and psychophysiology. However, by the end of the nineteenth century the core features and the boundaries of delirium were defined close to modern definition. Moreover, an effort was made to differentiate delirium, due to a wide range of organic diseases, from similar psychopathological states marked by clouding of consciousness.

The development of general hospital psychiatry in the twentieth century offered psychiatrists the opportunity to become better acquainted with the psychiatric complications of physical illness, of which delirium is the most common. With the appearance of the work of Bonhoeffer an important development in the area of psychopathology due to somatic diseases took place. He introduced the 'exogenous reaction types', including delirium, epileptiform excitement, twilight state, hallucinosis and amentia as a single class of nonspecific, acute mental concomitant of physical illness. 'Exogenous' implied an origin of the disorder in the body outside the brain, as a result of systemic diseases. They differed symptomatically from the 'endogenous' or functional mental disorders. The main psychopathological feature showed by most exogenous reaction types was a clouding of consciousness. Bonhoeffer, contrary to his contemporaries, recognized that there was not such a thing as disease-specific mental syndromes. In the decades that followed, it became clear that not only acute systemic diseases but also the primary cerebral ones, as well as intoxication by various drugs and poisons could give rise to one of the exogenous reaction types. By this time amentia, epileptic excitement and twilight states were no longer reckoned among the exogenous reaction types and only the terms 'delirium' and 'hallucinosis' survived till nowadays. Moreover, the importance of clouding of consciousness as a core feature of psychiatric complications of somatic diseases decreased.

In the first half of the twentieth century some clinicians addressed the pathogenesis and pathophysiology of delirium, both crucially important yet neglec-

ted aspects. It was recognized that nothing was known of the precise processes by which delirium was mediated, although in the great majority of cases the primary causal factors were supposed to be 'organic' and to consist in a modification of brain substance produced either by a toxin or a degenerative process. Robinson drew attention to the common occurrence of delirium in the elderly and proposed that cerebral arteriosclerosis and general aging of the brain lowered its metabolism and rendered it more susceptible to a variety of endogenous and exogenous toxic agents, which reduced its metabolic rate even further. He is probably the first writer to acknowledge the crucial role of 'cerebral oxidative metabolism' in the pathogenesis of delirium, a hypothesis further developed and tested in the 1940s.

The first scientific inquiry into the pathophysiological mechanisms underlying delirium was done by Engel and Romano, two very important pioneers in the field of delirium, who attempted to correlate clinical, psychological and encephalographic (EEG) data in patients with delirium due to a variety of systemic diseases. Their findings led them to the following conclusions. Delirium was a disturbance in the level of consciousness, established clinically by patient's responses to tests of cognition. The syndrome depended on the presence of a cerebral disorder indicated by the general slowing of the EEG background activity. A lowering of the rate of brain metabolism was a necessary condition for the EEG slowing and the concomitant cognitive impairment, both of which tended to vary simultaneously: the greater the slowing, the more profound the degree of impairment. Psychiatric symptomatology of delirium reflected fluctuations in the level of awareness (consciousness). Those psychological variables that correlated best with the slowing of the EEG background activity included attention, memory and comprehension. Manifest behaviour of a delirious patient might range from overactivity and hyperarousal to lethargy and stupor. Application of the work of Engel and Romano to all clinical variants of delirium was challenged, since the slowing of EEG background activity proved to be absent in delirium tremens.

In the last 40 years there have been no breakthroughs in research on delirium. The most important studies were those on 'experimental' delirium, induced by various anticholinergic agents. Those investigations highlighted the role of the disturbed balance of cerebral neurotransmitters, notably acetylcholine and noradrenaline, in the pathogenesis of delirium and hence created an important new approach to the scientific inquiry into this subject.

Since 1967 with the publication of his first article on delirium 'Delirium, clouding of consciousness and confusion' [2], Lipowski has made a great effort to summarize all the knowledge about delirium that had accumulated over the centuries and to review critically the relevant terminology in order to bring some order to it [1,3-7]. He also proposed a new classification of organic mental (brain) syndromes, that was largely adopted in the third edition of the classification of mental disorders of the American Psychiatric Association, published in 1980 [8]. Delirium was firmly established as one of the organic mental syndromes and for the first time explicit criteria for its diagnosis were

offered. As Lipowski argues "The ground for the much-needed research on the syndrome has been prepared".

REFERENCES

1. Lipowski ZJ. Delirium: Acute Confusional States. New York: Oxford University Press, 1990.
2. Lipowski ZJ. Delirium, clouding of consciousness and confusion. J Nerv Ment Dis 1967; 145: 227-255.
3. Lipowski ZJ. Delirium updated. Comprehensive Psychiatry 1980; 21: 190-196.
4. Lipowski ZJ. Transient cognitive disorders (Delirium, Acute Confusional States) in the elderly. Am J Psychiatry 1983; 11: 1426-1436.
5. Lipowski ZJ. Delirium (Acute Confusional States). JAMA 1987; 258: 1789-17 92.
6. Lipowski ZJ. Delirium in the elderly patient. New England Journal of Medicine 1989; 320: 578-582.
7. Lipowski ZJ. Delirium: Acute Brain Failure in Man. Springfield, Ill, Charles C Thomas, 1980.
8. Diagnostic and Statistical Manual of Mental Disorders, ed 3. Washington, DC, American Psychiatric Association, 1980.

Chapter 1.2

DIAGNOSIS AND SYMPTOMATOLOGY OF DELIRIUM

DEFINITION

Delirium is defined as a transient organic mental syndrome of acute onset, characterized by a global impairment of cognitive functions, a reduced level of consciousness, attentional abnormalities, increased or decreased psychomotor activity, and a disordered sleep-wake cycle [1-4]. Although the essential clinical features have been consistently described for centuries, the clinical presentation may be quite variable.

Table

DSM-III-R diagnostic criteria for delirium

A. Reduced ability to maintain attention to external stimuli (e.g., questions must be repeated because attention wanders) and to appropriately shift attention to new external stimuli (e.g., perseverates answer to a previous question).

B. Disorganized thinking, as indicated by rambling, irrelevant, or incoherent speech.

C. At least two of the following:
   1) reduced level of consciousness, e.g., difficulty keeping awake during examination
   2) perceptual disturbances: misinterpretations, illusions, or hallucinations
   3) disturbance of sleep-wake cycle with insomnia or daytime sleepiness
   4) increased or decreased psychomotor activity
   5) disorientation to time, place, or person
   6) memory impairment, e.g., inability to learn new material, such as the names of several unrelated objects after five minutes, or to remember past events, such as history of current episode of illness

D. Clinical features develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day.

E. Either (1) or (2):
   1) evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
   2) in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g., Manic Episode accounting for agitation and sleep disturbance

A standard description of delirium and explicit criteria for its diagnosis were provided by the publication of the DSM-III and the DSM-III-Revised in 1980 and 1987 respectively [2,3]. According to the DSM-111-R the essential features are reduced ability to maintain attention to external stimuli and to appropriately shift attention to new external stimuli and disorganized thinking, as manifested by rambling, irrelevant or incoherent speech. The syndrome also involves a reduced level of consciousness, sensory misperceptions, disturbances of the sleep-wake cycle and level of psychomotor activity, disorientation to time, place or person and memory impairment (table 1). The onset is relatively rapid and the course typically fluctuates. The total duration is usually

brief [3]. As Lipowski argues these criteria should be regarded as guidelines for diagnosis, because if examined more closely, only two psychopathological features must be present: attentional disorder and disorganized thinking [1].
On the other hand, the current draft of the tenth revision of the International Classification of Diseases (ICD-10) [4] offers more precise and stricter guidelines for the diagnosis of the syndrome, describing delirium as an etiologically nonspecific organic cerebral syndrome characterized by:

1. Impairment of consciousness and attention
2. Global disturbance of cognition
3. Psychomotor disturbances
4. Disturbance of the sleep-wake cycle
5. Emotional disturbances.

These disturbances occur concurrently and are of variable duration. The degree of severity ranges from mild to very severe [1,4]. Thus, contrary to the DSM-III-R the ICD-10 requires all features to be present for diagnosing delirium. It will, therefore, be more clear what is meant by a diagnosis of delirium. The ICD-10 criteria are probably more specific, but less sensitive than the DSM-III-R criteria and better to operationalize.

CLINICAL FEATURES AND VARIANTS

The symptoms of delirium have been extensively described by many clinicians in a number of reviews [1,5-11]. Abnormalities in every aspect of the mental state have been found in association with delirium. The full-blown syndrome may be preceded by *prodromal symptoms*, usually beginning with insomnia by night and drowsiness by day, vivid and often disturbing frightening dreams, transient illusions and hallucinations, and brief moments of disorientation. When awake there is an increasing difficulty to concentrate and to think clearly. The patient may become restless, irritable and anxious or more lethargic and withdrawn. He may report hypersensitivity to sensory stimuli, fatigue and malaise [1,8,11]. The patient may never progress beyond the prodromal stage, or the symptoms may increase in intensity and a full-blown delirium develops [1]. Certain characteristics of delirium make its recognition, especially in the early stages more difficult: The onset often occurs at night and its development is in general relatively rapid, over hours or days. The clinical manifestations are fluctuating, with lucid intervals in the morning and maximum disturbance at night when the patient is fatigued and sensory input reduced [1,8,11,15]. However, as Lipowski points out: "In general, acute onset of cognitive and attentional deficits and abnormalities, whose severity fluctuates during the day and tends to increase at night, is practically diagnostic" [1,8,9]. In delirium the main aspects of cognition (thinking, perception and memory) are all disturbed in some degree, hence the term 'global' [1,7-9,11].
The disordered *thinking* may be revealed by a rambling, disorganized and incoherent speech. Sometimes patients may become mute. Spontaneous utterances tend to be stereotyped and perseverated. The speech volume ranges from whispered muttering to shouting and screaming [11]. A deterioration of wri-

ting ability is common, probably being a sensitive indicator of delirium [6,11]. If the delirium is light, the only abnormality may be a slowing down or speeding up of the stream of thought, but as it becomes more severe the capacity to make judgements, to grasp abstract concepts and to reason logically are all impaired [11]. The content of thought may also be disturbed in delirium. Fleeting, poorly organized delusions of a persecutory nature are often, but not invariably, present and are influenced by environmental stimuli. The patient may be suspicious of and feel threatened by the medical staff. For example, he may think that he is being poisoned and as a consequence not take his medication and behave combative.

Perception is often abnormal and although hallucinations are common in delirium, they are not an essential feature of the syndrome. A wide range of perceptual distortions, illusions and hallucinations can occur, which are most often visual or both visual and auditory [6-9,11]. Patients may perceive objects around them too small (micropsia), too big (macropsia) or otherwise distorted (dysmorphopsia) [7,11]. Hallucinations of all degrees of complexity occur, from simple flashing lights and noises to three-dimensional, moving, vivid, coloured images of people, animals and objects and to voices [7,8,11]. Hallucinations may be closely related with delusions, tend to be terrifying and can make the patient hostile, fearful and aggressive [6-9]. Although tactile hallucinations are less common than visual and auditory ones, they may occur [8,11]. Illusions and hallucinations appear more commonly when the sensory input is reduced or ambiguous, for example at night and in patients with pre-existing visual and auditory impairment [11].

Memory is disturbed in all its key aspects: registration, retention and recall. In particular, the impaired registration of new experience, due to short attention-span, results in learning deficits and anterograde amnesia [6,8-11]. Once delirium has remitted, there is usually a partial or complete amnesia for the period of delirium, but certain psychotic experiences may be recalled [11]. Impairment of remote memory is less common in delirium, but may be disturbed in more severe cases [11]. The patient may confabulate to make up for memory [8,11].

Impairment of *attention*, with hypo- or hyperalertness, is a core feature of delirium and invariably present in some degree [1-13]. The attentional deficit results in decreased concentration and distractibility.

The combination of a global cognitive disturbance and a disordered attention appear to be responsible for the often rapidly developing *disorientation* in severe delirium, first in time and subsequently also in place and person (i.e. the misidentification of familiar persons). In mild cases, however, orientation may be intact [1,6-13].

Since *wakefulness* is often reduced during the day, the patient then often dozes off, while mostly at night he is coming to live and becomes agitated and hyperactive. The normal *sleep-wake* cycle is always disrupted and often completely reversed, worsening even more the cognitive-attentional deficits [6-9]. Sometimes the patient hardly sleeps at all, being persistently hyperalert. An episode of nocturnal disturbance often is the first sign of impending deli-

rium, while conversely, the restoration of quiet sleep heralds improvement [11].
With respect to *psychomotor behaviour* patients may show hyperactive as well as hypoactive symptoms with regard to their movements and speech. For the most part overactivity in delirium is purposeless and repetitive such as the persistent plucking and picking at bedclothes. Sometimes patients show more complex stereotyped movements, the so-callled 'occupational delirium', since these stereotypes often represent habitual, work-related activities [11]. Restless wandering and physical and verbal aggressive outbursts may create the greatest management problems [11]. The hyperactive patient easily becomes exhausted or will harm himself otherwise, not feeling much pain while delirious, for example by falling or pulling out lines. The agitation is usually associated with overactivity of the sympathetic nervous system.
This type of delirium is called the *hyperalert-hyperactive type* (similar to the ancient syndrome 'phrenitis') and is typically seen in withdrawal (from alcohol or certain drugs like benzodiazepines) delirium [1,9,11,13-15].
By contrast, the *hypoalert-hypoactive type* (similar to the ancient syndrome 'lethargus') of delirium is characterized by a reduced level of activity and alertness. The patient responds only slowly and with hesitation to stimuli, he is quiet, speaks little and displays diminished psychomotor activity. Especially older patients and probably patients with a metabolic encephalopathy are prone to this type of delirium and are often misdiagnosed as depressed [1,9,11,13-15].
The *mixed type* of delirium features unpredictable shifts from reduced alertness and activity to hyperalertness and overactivity, and vice versa [1,9,14].
Lately, two studies have been published trying to validate the clinical impressions of the frequency and characteristics of these subtypes of delirium [14,15]. Liptzin and Levkoff daily evaluated 325 elderly patients, admitted to a general hospital for an acute medical problem, in order to detect symptoms of delirium. In the 125 patients with delirium the three aforementioned subtypes of delirium could be identified on the basis of a certain symptom-pattern. The mixed type proved to be the most common (52%), followed by the hypoactive type (19%) and the hyperactive type (15%). Fourteen percent of the patients had neither hyper- nor hypoactivity. There were no statistically significant differences between the different groups. However, the hyperactive group had a shorter length of stay and a lower mortality rate than both the hypoactive and mixed group [14]. This interesting research requires further investigation into the relation of these clinical subtypes of delirium and certain underlying medical illness and, possibly, correlation with findings from electroencephalography [14].
Ross et al., although in a somewhat less systematic way, also found that phenomenologic subtypes of delirium can be defined on the basis of level of alertness. Positive symptoms, such as hallucinations, illusions and delusions were strongly related with agitation and appeared to be more common in patients with the hyperactive type of delirium [15]. Scores for depression and elation did not differ between the two groups. Somnolent (hypoactive) patients were about twice as prevalent as activated patients [15]. Since the patients were eva-

luated only once, the stability of the clinical subtypes of delirium could not be assessed [15]. This may also be the reason for not including the mixed type of delirium, creating a bias in the frequency of the two other subtypes. In some patients phenomenology was related to etiology: all patients with hepatic encephalopathy had the somnolent subtype of delirium, while fever was approximately equally associated with each of the two subtypes [15].
Delirium is usually accompanied by profound *affective changes*, ranging from fear, depression, apathy, anger, rage to euphoria [1,2-13]. Fear and apathy are regarded as the most prominent affects in delirium [1,11]. It is generally accepted that premorbid personality, mood state, life-events and circumstances all have an impact on the nature and extent of affective responses in delirium, but relationships between these and delirium have never been adequately documented.
Incontinence of urine and faeces is usual in severe cases and some patients may show involuntary movements such as asterixis or coarse tremor [1,11].

DIAGNOSIS

Delirium is in fact easy to diagnose. First, the syndrome has to be recognized on the basis of its characteristic clinical features and second, the underlying organic etiological factor(s) must be identified by means of a general medical history, a physical examination and appropriate laboratory tests [1]. It is essential to examine the cognitive functioning of the patient and to observe his behaviour more or less constantly. Electroencephalography can be of aid in diagnosing delirium since it typically shows diffuse slowing of the background activity, though such slowing occurs also in Alzheimer's disease and is absent in alcohol and drug delirium. In general, the diagnosis is made primarily on clinical grounds [1,13].

Delirium is, by definition, a transient syndrome, but this does not imply that it is always followed by complete recovery [1-4]. Depending on the underlying cause the patient will survive and return to the premorbid state, be left with some form or degree of psychological impairment or die [1]. The most common outcome is full recovery. However, delirious patients are, compared with patient control groups, more at risk for both in-hospital as post-discharge death, longer hospitalization and institutionalization [1,13,16-18]. The higher mortality rate found in patients with delirium appears to depend more on the medical condition than on the presence of delirium [13,16.18].

REFERENCES

1. Lipowski ZJ. Delirium: Acute Confusional States. New York: Oxford University Press, 1990.
2. Diagnostic and Statistical Manual of Mental Disorders, ed 3. Washington, DC, American Psychiatric Association, 1980.
3. Diagnostic and Statistical Manual of Mental Disorders, ed 3 revised. Washington, DC, American Psychiatric Association, 1987.
4. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva, World Health Organization, 1992.
5. Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. J Chronic Dis 1959; 9:

260-277.
6. Lipowski ZJ. Delirium updated. Comprehensive Psychiatry 1980; 21: 190-196.
7. Lipowski ZJ. Transient Cognitive Disorders (Delirium, Acute Confusional States) in the Elderly. Am J Psychiatry 1983; 11: 1426-1436.
8. Lipowski ZJ. Delirium (Acute Confusional States). JAMA 1987; 258: 1789-1792.
9. Lipowski ZJ. Delirium in the elderly patient. N Engl J Med 1989; 320: 578-582.
10. Rockwood K. Acute confusion in elderly medical patients. J Am Geriat Soc 1989; 37: 150-154.
11. Lindesay J, Macdonald A, Starke I. Delirium in the elderly. Oxford, Oxford University Press, 1990.
12. Miller NE, Lipowski ZJ (eds). Delirium. Advances in research and clinical practice. International Psychogeriatrics 1991; 3: 115-149.
13. Francis F, Kapoor WN. Delirium in the hospitalized elderly. J of General Internal Medicine 1990; 5: 65-79.
14. Liptzin B, Levkoff SE. An empirical study of delirium subtypes. Brit J Psychiatry 1992; 161: 842-845.
15. Ross CA, Peyser CE, Shapiro I, Folstein MF. Delirium: Phenomenologic and etiologic subtypes. International Psychogeriatrics 1991; 3: 135-147.
16. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990; 263: 1097-1101.
17. Thomas RI, Cameron DJ, Fahs MC. A prospective study of delirium and prolonged hospital stay. Arch Gen Psychiatry 1988; 45: 937-940.
18. Hemert AM van, Mast RC van der, Hengeveld MW, Vorstenbosch M. Excess mortality in general hospital patients with delirium. A 5-year follow-up of 519 patients seen in psychiatric consultation. J Psychosomatic Res 1994; 38: 153-154.

Chapter 2

DELIRIUM AFTER CARDIAC SURGERY: A CRITICAL REVIEW

R.C. van der Mast, F.H.J. Roest

INTRODUCTION

Since the mid 1950s numerous articles have been published concerning psychiatric complications, especially delirium, following cardiac surgery [1-57, table 1]. Cardiac surgery has traditionally been associated with a particularly high rate of postoperative delirium. The reported incidence varies from 2-57%, depending on the research design, the selection of patients, the type of cardiac surgery, the assessment methods and not least of all, the criteria and definition of delirium [1-57,table 1].

Blachly and Starr were the first to use the term postcardiotomy delirium for delirium after cardiac surgery [5]. They defined delirium referring to the presence of any evidence of organic symptoms, by which was meant a syndrome consisting of impairment of orientation, memory, intellectual functions and judgement, and of lability of affect. Originally, postcardiotomy delirium was associated with open-heart surgery (and extracorporeal circulation), but later on the term was also used for delirium after coronary artery bypass surgery. Yet, this procedure does not require the heart to be opened extensively, unlike the operation required to repair valvular and congenital defects [31]. So, less cardiac damage will be done and (micro) embolization, a possibly important insult to the brain, is less likely to occur. However, since postcardiotomy delirium is an established diagnostic term, we will use it for delirium after cardiac surgery, irrespective of the kind of operation.

The current incidence of postcardiotomy delirium is unknown and multiple studies have implicated as many risk factors. Smith and Dimsdale [58] reviewed the literature using meta-analysis to combine the results of 44 research studies, published between 1963 and 1987 in a variety of English-language journals. They examined the incidence of postcardiotomy delirium and the relationship with 28 hypothesized risk factors and came to the conclusion that the incidence has remained fairly constant over time at 32% [58]. Apart from preoperative psychiatric intervention, they did not find any substantial correlation between the occurrence of postcardiotomy delirium and any other risk variable. However, after revision of the studies used for meta-analysis, comment can be given on their methods and conclusions.

One of the main problems is the definition of delirium. According to current diagnostic standards, the DSM-III-(R) [59], the essential features of delirium are A. reduced ability to maintain attention to external stimuli and to appropriately shift attention to new external stimuli and B. disorganized thinking, as manifested by rambling, irrelevant or incoherent speech. The syndrome should also involve C. at least two of the following features: a reduced level of consciousness, sensory misperceptions, disturbances of the sleep-wake cycle or level of psychomotor activity, disorientation to time, place or person and memory impairment. D. The onset is relatively rapid and the course typically fluctuates. The total duration is usually brief, about one week. Although it is, of course, impossible to classify all the research studies according to current

diagnostic criteria, an effort has to be made to approach these current criteria as much as possible.

Smith and Dimsdale classified 'the various clinical presentations' of postcardiotomy delirium into three groups: group 1 including symptoms of disorientation to place or time, group 2 consisting of perceptual illusions, failure to recognize family or friends, or disorientation to identity and group 3 containing hallucinations, paranoid ideation or agitation [58]. Yet, such a classification does not represent the 'various clinical presentations', but different symptoms of delirium, in particular those symptoms mentioned under C. of the DSM-III-R [59]. None of these separate symptoms, as described in the three groups, is nowadays enough for a diagnosis of delirium.
Besides, there has been some debate on the time of onset of postcardiotomy delirium [58,60]. Some investigators, especially the group of Heller and Kornfeld, only favour a diagnosis of postcardiotomy delirium when the syndrome follows a lucid interval of 2-5 days postoperatively [5,8,22,31,39,40]. A similar syndrome, occurring before that time is classified as an organic brain syndrome, without mentioning the differences in clinical presentation. Others do not find such a 'lucid interval' or do not even mention the time of onset as a possibly important clinical feature of delirium after heart surgery [58].
Also, in some, but not or only partly in other studies, postoperative deaths were excluded resulting in a different incidence of postoperative delirium. Since we were unable to classify the psychiatric symptoms in most studies - some studies do not even define postoperative delirium-, we were puzzled by the methods the authors used to group apparently many of the 44 studies in as much as three categories. Because meta-analysis, a quantative method for reviewing reported studies, requires at least well defined, discrete endpoints- i.e. delirium, most of the reported studies are useless for this purpose [61]. The conclusion that delirium has remained fairly constant over time is therefore questionable.

Another problem is the selection of patients in the studies, used for the meta-analysis [58]. Studies using consecutive and selected patient samples of different age-ranges, gathered both retrospectively and prospectively by different methods of case finding -i.e. interview or chart review- were taken together (table 1).
Also, in the course of time the type of cardiac surgery studied shifted from surgery for valve and congenital lesions in the 60s and begin 70s to mainly coronary artery bypass surgery (with or without valve replacement) in the late 70s and 80s. Consequently, the patients samples changed with respect to, for example, gender and age distribution, surgical procedures and length of extracorporeal circulation. Did surgery for valve and congenital lesions concern mainly female patients, coronary artery bypass surgery was performed on male patients predominantly. Moreover, the mean age increased approximately 10 years over time.

Smith and Dimsdale used the vote-counting method described by Hedges and Olkin [61,62] to estimate the underlying population correlation between a risk factor and the incidence of postcardiotomy delirium from the collection of selected studies. This method, although appropriate when the only information available is whether a relationship was reported to be significant, yields a very crude estimate of the population correlation and therefore, confidence intervals should always be added. To be able to draw any reliable conclusions, at least ten studies are needed [62]. In the meta-analysis done by Smith and Dimsdale [58] this was only the case for age, gender and time on cardiopulmonary bypass. For example, if three studies are available describing the relationship between preoperative psychiatric intervention and postcardiotomy delirium [58], only three correlation estimates are possible: 0 when none or one of the three studies reports a significant relation, .06 when two studies report a significant relation and .60 when all three studies report a significant relation. In the last case, the 95% confidence interval for .60 ranges from 0 to 1 (only positive correlations are estimated), meaning that the population correlation can be anything from non-existent to perfect. This clearly demonstrates the need for sufficient studies reporting on a possible risk factor.
This leads to the problem of the power of the surveyed studies. The sample sizes are usually small, varying from 10 to 312, with only 6 out of 44 studies describing a sample size larger than 100 [58]. In a sample of 100 cases, a sample correlation has to be larger than .20 to be significant. In a complex syndrome like postcardiotomy delirium, the correlation between a risk factor and the event may typically be lower than .20 or in terms of odds ratios, the relative risk may be lower than 1.5.
Another problem is the publication bias. Non-significant results are either not reported at all or the test results are not given. For example, most studies will have at least recorded the age and gender of their patients and, in most cases, have tested for a significant relationship. Nevertheless, in many studies not even the mean age and/or gender distribution are reported.

All these circumstances make it, in our opinion, impossible to take the different studies on delirium after cardiac surgery together for a meta-analysis as reported by Smith and Dimsdale. Consequently, their conclusion [58] that the incidence of postcardiotomy delirium has remained fairly constant over time at 32% and that, of all the surveyed risk factors, only preoperative psychiatric intervention correlated substantially with postcardiotomy delirium, is unfounded. Therefore, we selected those studies on postcardiotomy delirium in which delirium was well defined and more or less comparable to current criteria [59] and examined the possibilities for further analysis of incidence and risk factors.

METHODS

The 44 research studies analyzed by Smith and Dimsdale [4-6,8-16,18,21-31,33,35-45,47-54] were investigated. A literature search was done for the period between 1988 and 1994, yielding three more studies on postcardiotomy delirium [55-57]. Another ten studies, reporting on the relation between car-

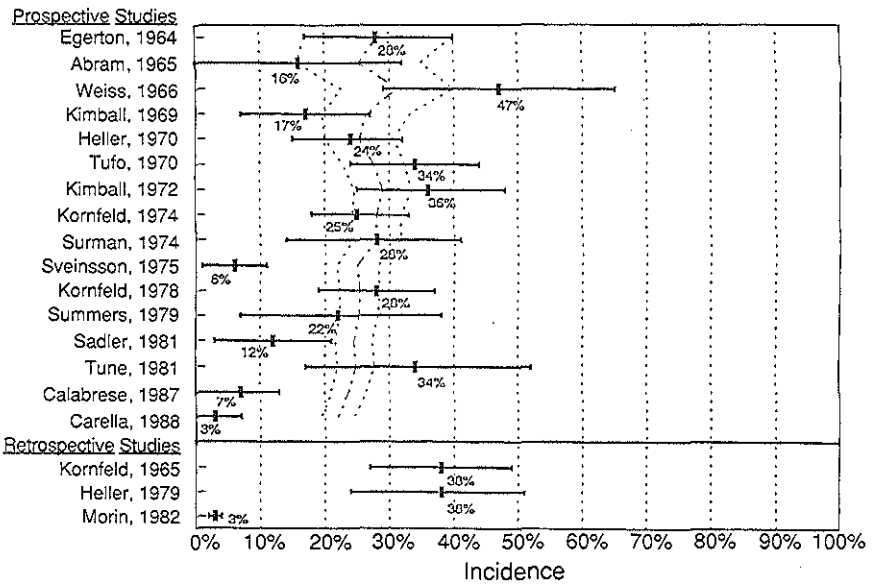
diac surgery and the occurrence of postoperative delirium [1-3,7,17,19,20, 32,34,46], not used by Smith and Dimsdale, were found in the references. Of those studies using (partly) the same study sample, the most adequate (e.g. the one used by Smith and Dimsdale) and detailed one was taken for further examination. Those studies in which postcardiotomy delirium was well-defined and met more or less the current DSM-III-R criteria [59] were selected. For example, the group of Heller and Kornfeld judged patients to have a delirium when, after a lucid interval of two to five days, they developed illusions, frequently accompanied by difficulty distinguishing between dreams and reality, often with disorientation and sometimes progressing to hallucinations and delusions. Although in this definition the attentional disorder and the disorganized thinking in the narrow sense are lacking and the necessity of a 'lucid interval' after surgery before the occurrence of the postoperative delirium is introduced, such a definition was considered adequate. In the studies mentioning 'organic brain syndromes' to classify delirium-like and/or neurological symptoms [22,31,39,51], these were not included since it was impossible to distinguish 'true' postcardiotomy delirium. Retrospective studies in which delirium was well defined were regarded separately. Studies reporting on selected patient samples were excluded as well as studies which gathered patient samples both retro- and prospectively without specifying where the data came from. In one study including children younger than 16 years, we separated them from the adult patients, only using the information of the adult patients [36]. The selected studies were scrutinized and as far as possible analyzed for incidence and risk factors of postcardiotomy delirium.

RESULTS

Most, namely 28, of the 44 studies used by Smith and Dimsdale for analysis of the overall incidence did not describe delirium at all or sufficiently enough to draw any conclusions [4,5,9,11-16,18,21,25-29,35,37,38,41,43,47-52,54]. In 15 studies postcardiotomy delirium was rather well defined [6,8,10,22-24,30, 33,36,39,40,42,44,45,53]. These studies were supplemented with an adequately defined study published after 1987 [55] and two (out of ten) studies found in the literature [7,19]. An overview of all the studies is shown in table 1. Four pairs of studies apparently used (partly) the same patient sample [5/13,30/32,35/37 and 41/44]. Only two pairs of studies [30/32 and 41/44] used well-defined criteria, from which the most adequate ones were chosen for further examination [30,44]. Six studies reporting on selected patient samples or gathering patient samples both retro- and prospectively were excluded [15,21,24, 29,47,56]. This yielded a total of 16 prospective [6,10,17,19,22, 23,30,33,36,39,40,42,44,45,53,55] and 3 retrospective [8,40,46] studies for further research and analysis of an overall incidence of postcardiotomy delirium and possible risk factors.

Figure 1 shows the incidences of delirium reported in the 16 prospective and 3 retrospective studies we selected. For each incidence the confidence interval was computed, based on the sample size of the study. The incidences vary

Figure 1
Incidences and confidence intervals of delirium after cardiac surgery



considerably and the small overlap of the confidence intervals is a clear sign of the heterogeneity of the studies. This means that not all samples are drawn from the same population. An important assumption for statistical meta-analysis is therefore not met. Regression analysis was used to test the hypothesis that this heterogeneity is due to reported differences between the studies like year of publication, type of surgery, mean age and gender distribution. Although the heterogeneity of the patient samples could not be explained, a significant relationship was found between year of publication and incidence of postcardiotomy delirium ($t=-2.11$, $df=14$, $p=.05$), the later publications showing a tendency towards a lower incidence. Since there appeared only three retrospective studies just incidences and confidence intervals can be given. The big difference between on the one hand the studies of Kornfeld and Heller and on the other hand Morin is explained by the different methods used and the sample sizes (see table 1) [8,40,46]. Even though results on the effect of the possible risk factors age, gender and time on cardiopulmonary bypass were reported frequently enough, we decided not to perform a statistical meta-analysis, since the assumption of homogeneity was not met.

DISCUSSION

Even after 30 years and more than 50 studies addressing in some way the issue of incidence of and risk factors for delirium after cardiac surgery, this question remains unanswered. A few reasons for this can be pointed out.

First of all, since the criteria have evolved over time, delirium is not equally defined in the studies reporting on postcardiotomy delirium or, even worse, is not defined at all, making it difficult to compare the various studies. For example, of the 29 studies having postoperative delirium as (the most important) outcome measure, 12 (41%) studies do not use an adequate definition of delirium (table 1). An important unresolved and difficult issue in this respect is the operationalization of the diagnostic criteria to ensure reliability of research findings and to allow replicability [63]. In none of the described studies the criteria for postoperative delirium are explicitly operationalized.
Second, consecutive patient samples appear to be no guarantee for homogeneity of the various studies. Other factors like the kind of hospital, the area served, the number of beds, the experience of the surgeons and the in- and exclusion criteria used, often not sufficiently specified, are probably influencing the incidence. Of all the reported differences in the studies, only the year of publication is significantly related to the incidence of delirium after cardiac surgery, the later publications showing a tendency towards a lower incidence. Contrary to the conclusion of Smith and Dimsdale, this may be in line with the clinical notion that the incidence of postcardiotomy delirium has declined, possibly due to improved surgical and cardiopulmonary bypass techniques.
Furthermore, it is hard to judge the statistical merits of the studies when the data and statistical techniques are insufficiently described. An example of poor statistical quality is the article of Tufo et al [23]. They report the relationship between cerebral damage and age groups to be highly significant, which it is not when the frequencies in the accompanying table can be trusted. Also contrary to the reported result, the relation between cerebral damage and blood pressure during bypass appears to be significant. In general, the statistical results could not be reproduced from the reported data. This seriously hampers statistical meta-analysis.

In conclusion, most of the results of the studies reporting on postoperative delirium after cardiac surgery are not comparable. Nevertheless, the careful conclusion may be drawn that no strong risk factor has been identified and that, even if prospective studies using consecutive patient samples with more or less well-defined criteria for delirium are selected, the incidence of postcardiotomy delirium has probably decreased.

REFERENCES

1. Fox HM, Rizzo ND, Gifford S, et al: Psychological observations of patients undergoing mitral surgery. Psychosom Med 1954; 16: 186-208.
2. Priest WS, Zaks MS, Yacorzynski GK, et al: The neurologic, psychiatric, and psychologic aspects of cardiac surgery. Med Clin North Am 1956; 41: 155-169.
3. Dencker SJ, Sandahl A: Major mental disturbances in a series of patients surgically treated for mitral stenosis. Acta Psychiatr Scand 1962; 38: 117-123.
4. Knox SJ: Psychiatric aspects of mitral valvotomy. Br J Psychiatry 1963; 109: 656-668.
5. Blachly PH, Starr A: Post-cardiotomy delirium. Am J Psychiatry 1964; 121: 371-375.
6. Egerton N, Kay JH: Psychological disturbance associated with open-heart surgery. Br J

Psychiatry 1964; 110: 443-449.
7. Abram HS: Adaptation to open heart surgery. A psychiatric study of response to the threat of death. Am J Psychiatry 1965; 122: 659-667.
8. Kornfeld DS, Zimberg S, Malm JR: Psychiatric complications of open-heart surgery. N Engl J Med 1965; 273: 287-292.
9. Blachly PH, Kloster FE: Relation of cardiac output to postcardiotomy delirium. J Thorac Cardiovasc Surg 1966; 52: 422-427.
10. Weiss SM: Psychological adjustment following open-heart surgery. J Nerv Ment Dis 1966; 143: 363-368.
11. Burgess GN, Kirklin JW, Steinhilber RM: Some psychiatric aspects of intracardiac surgery. Mayo Clin Proc 1967; 42: 1-12.
12. Gilberstadt H, Sako Y: Intellectual and personality changes following open-heart surgery. Arch Gen Psychiatry 1967; 16: 210-215.
13. Sachdev NS, Carter CC, Swank RL, et al: Relationship between postcardiotomy delirium, clinicial neurological changes, and EEG abnormalities. J Thorac Cardiovasc Surg 1967; 54: 557-563.
14. Edington HC: Open-heart surgery: a triple threat. South Med J 1968: 61: 160-166.
15. Lazarus HR, Hagens JH: Prevention of psychosis following open-heart surgery. Am J Psychiatry 1968: 134: 1190-1195.
16. McClish A, Andrew D, Tetreault L: Intraveneous diazepam for psychiatric reactions following open-heart surgery. Can Anaesth Soc J 1968; 15: 63-79.
17. Henrichs TF, Mackenzie JW, Almond CH: Psychological adjustment and acute response to open-heart surgery. J Nerv Ment Dis 1969; 148: 158-164.
18. Javid H, Tufo HM, Najafi H, et al: Neurological abnormalities following open-heart surgery. J Thorac Cardiovasc Surg 1969; 58: 502-509.
19. Kimball CP: Psychological responses to the experience of open heart surgery. I. Am J Psychiatry 1969; 126: 96-107.
20. Morse M, Litin EM: Postoperative delirium. A study of etiologic factors. Am J Psychiatry 1969; 126: 388-395.
21. Rubinstein D, Thomas JK: Psychiatric findings in cardiotomy patients. Am J Psychiatry 1969; 126: 108-117.
22. Heller SS, Frank KH, Malm JR, et al: Psychiatric complications to open-heart surgery. N Engl J Med 1970; 283: 1015-1020.
23. Tufo HM, Ostfeld AM, Shekelle R: Central nervous system dysfunction following open-heart surgery. JAMA 1970; 212: 1333-1340.
24. Danilowitz DA, Gabriel HP: Postcardiotomy psychosis in non-English-speaking patients. Psychiatry Med 1971; 2: 314-320.
25. Freyhan FA, Gianelli S Jr, O'Connell RA, et al: Psychiatric complications following open heart surgery. Compr Psychiatry 1971; 12: 181-195.
26. Layne OL, Yudofsky SC: Postoperative psychosis in cardiotomy patients. N Engl J Med 1971; 284: 518-520.
27. Lee WH, Brady MP, Rowe JM, et al: Effects of extracorporeal circulation upon behavior, personality, and brain function. Ann Surg 1971; 173: 1013-1023.
28. Morgan DH: Neuro-psychiatric problems of cardiac surgery. J Psychosom res 1971; 15: 41-46.
29. Blacher RS: The hidden psychosis of open-heart surgery. JAMA 1972; 222: 305-308.
30. Kimball CP: The experience of open heart surgery, 3: toward a definition and understanding of postcardiotomy delirium. Arch Gen Psychiatry 1972; 27: 57-63.
31. Kornfeld DS, Heller SS, Frank KA, et al: Personality and psychological factors in postcardiotomy delirium. Arch Gen Psychiatry 1974; 31; 249-253.
32. Quinlan DM, Kimball CP, Osborne F: The experience of open-heart surgery. Arch Gen Psychiatry 1974; 31: 241-244.
33. Surman OS, Hackett TP, Silverberg EL, et al: Usefulness of psychiatric intervention in patients undergoing cardiac surgery. Arch Gen Psychiatry 1974; 30: 830-835.
34. Kilpatrick DG, Miller WC, allain AN, et al: The use of psychological test data to predict open-heart surgery outcome. A prospective study. Psychosom Med 1975; 37: 62-73.
35. Rabiner CJ, Willner AE, Fishman J: Psychiatric complications following coronary bypass surgery. J Nerv Ment Dis 1975; 160: 342-348.
36. Sveinsson IS: Postoperative psychosis after heart surgery. J Thorac Cardiovasc Surg 1975; 70: 717-725.
37. Willner AE, Rabiner CJ, Wisoff BG, et al: Analogy tests and psychopathology at follow-up

after open heart surgery. Biol Psychiatry 1976; 11: 687-696.
38. Merwin SL, Abram HS: Psychologic response to coronary artery bypass. South Med J 1977; 70: 153-155.
39. Kornfeld DS, Heller SS, Frank KA, et al: Delirium after coronary artery bypass surgery. J Thorac Cardiovasc Surg 1978; 76: 93-96.
40. Heller SS, Kornfeld DS, Frank KA, et al: Postcardiotomy delirium and cardiac output. Am J Psychiatry 1979; 136: 337-339.
41. Sadler PD: Nursing assessment of postcardiotomy delirium. Heart Lung 1979; 8: 745-750.
42. Summers WK: Psychiatric sequelae to cardiotomy. J Cardiovasc Surg 1979; 20: 471-475.
43. Kollka R, Hilberman M: Neurologic dysfunction following cardiac operation with low-flow, low-pressure cardiopulmonary bypass. J Thorac Cardiovasc Surg 1980; 79: 432-437.
44. Sadler PD: Incidence, degree, and duration of postcardiotomy delirium. Heart Lung 1981: 10: 1084-1091.
45. Tune LE, Damlouji NF, Holland A, et al: Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981; 2: 651-653.
46. Morin P, Coupal P: Delirium post-chirurgie cardiaque avec circulation extra-corporelle: aspects cliniques et observations dans un centre spécialisé. Can J Psychiatry 1982; 27: 31-39.
47. Owens JF, Hutelmyer CM: The effect of preoperative intervention on delirium in cardiac surgical patients. Nurs Res 1982; 31: 60-62.
48. Slogoff S, Gigis KZ, Keats AS: Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass. Anesth Analg 1982; 61: 903-911.
49. Naber D, Bullinger M: Neuroendocrine and psychological variables relating to post-operative psychosis after open-heart surgery. Psychoneuro-endocrinology 1985; 10: 315-324.
50. Quinless FW, Cassese M, Atherton N: The effect of selected preoperative, intraoperative, and postoperative variables on the development of postcardiotomy psychosis in patients undergoing open heart surgery. Heart Lung 1985; 14: 334-341.
51. Shaw PJ, Bates D, Cartlidge NEF, et al: Early neurological complications of coronary artery bypass surgery. Br Med J 1985; 291: 1384-1387.
52. Nussmeier NA, Arlund C, Slogoff S: Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 1986: 64: 165-170.
53. Calabrese JR, Skwerer RG, Gulledge AD, et al: Incidence of postoperative delirium following myocardial revascularization. Cleve Clin J Med 1987; 54: 29-32.
54. Harrell RG, Othmer E: Postcardiotomy confusion and sleep loss. J Clin Psychiatry 1987; 48: 445-446.
55. Carella F, Traviani G, Contri P, et al.: Cerebral complications of coronary by-pass surgery. A prospective study. Acta Neurol Scand 1988; 77: 158-163.
56. Edmunds LH, Stephenson LW, Edie RN, Ratcliffe MB: Open-heart surgery in octogenarians. N Engl J Med 1988; 319: 131-136.
57. Folks DG, Freeman AM, Sokol RS, Govier AV, Reves JG, Baker DM: Cognitive dysfunction after coronary bypass surgery: A case-controlled study. South Med J 1988; 81: 202-206.
58. Smith LW, Dimsdale JE. Postcardiotomy Delirium: Conclusions after 25 Years? Am J Psychiatry 1989; 146: 452-458.
59. Diagnostic and Statistical Manual of Mental Disorders, ed 3 revised. Washington, DC, American Psychiatric Association, 1987.
60. Lipowski ZJ. Delirium: Acute Confusional States. New York: Oxford University Press, 1990.
61. Greenland S. Qantitative methods in the review of epidemiologic literature. Epidemiologic Reviews 1987; 9: 1-30.
62. Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, Fla, Academic Press 1985.
63. Levkoff S, Liptzin B, Cleary P, Reilly CH, Evans D. Review of research instruments and techniques used to detect delirium. In: Delirium. Advances in research and clinical practice. International Psychogeriatrics 1991; 3: 253-271.

Table 1
Delirium after cardiac surgery: a review of the literature

author	year	no.of patients	♂/♀	mean age	selection	methods	incidence
Fox◆[1]	1954	32	9/23	37 median	24-49 years; mitral surgery	prospective; pre-and post-OP psychiatric interview (no objective measures)	18.8%
Priest◆[2]	1957	60	±1:2	?	22-60 years; surgery for aortic-, mitral valve, septal and congenital lesions	prospective; pre-OP: neurologic, psychiatric and psychometric evaluation (different instruments); post-OP: after operation neurologic and psychiatric evaluation, retesting after 6,12,24 months	?
Dencker◆[3]	1962	61	15/46	40.1	17-53 years; consecutive; mitral commissurotomy	retrospective study of records	4.9%
Knox◆[4]	1963	1) 50 2) 40	6/44 10/30	34.1 36.9	consecutive; surgery for mitral valve lesions	1)retrospective; study of records, psychiatric interview 2)prospective; pre-and post-OP psychiatric assessment (day 2+7, after 3 months); pre-and post-OP psychometric tests	1) 2% 2) 2.5%
Blachly+◆[5]	1964	139 (164)*	1:1	?	≥15 years; consecutive; variable heart-and great vessels surgical procedures; excl.patients who died within 7 days postoperatively	prospective; pre-OP+post-OP psychiatric evaluation (checklist, regularly) incl. information staff	57% (48%)*
Egerton[6]	1964	60 (90)*	?	39	>18 years; consecutive; surgery for aortic,mitral and congenital lesions; excl.patients who died	prospective; pre-OP+post-OP standardized information on mental status 5x/week	n=17=28%,if> 12hrs and >1 symptom
Abram◆[7]	1965	19 (23)*	15/8	44	16-62 years; cardiac surgery for valve and septal lesions, resection aneurysm	prospective; pre-and post psychiatric interview	n=3=16%
Kornfeld[8]	1965	99, but 79 adults	?	±39 incl. 20 children	adults; open-heart surgery for aortic, mitral and congenital lesions	retrospective (chart-review of any sign of delirium by staff); 20 of the patients were interviewed after having left the recovery room (±6 days post-OP)	38%
Blachly◆[9]	1966	37	?	?	aortic, mitral and multiple valve replacement	retrospective (chart review for presence of 'brain syndrome' or 'hallucinosis' ?); pre-and post-OP: cardiac output	?
Weiss[10]	1966	30	?	41.3	16-60 years; open-heart surgery excl. patients with a psychiatric history	prospective; pre-OP: various psychometric instruments, measuring personality traits, cognitive function, level of anxiety and seriousness of illness; post-OP: mental status examination every other day+information staff	n=14=46.6%
Burgess[11]	1967	36	19/15	±38	cardiac surgery for valve and congenital lesions	prospective; pre-and post-OP interview	27.8%
Gilberstadt◆[12]	1967	52	all ♂	48	open-heart surgery	prospective; pre-OP+post-OP (after three weeks) testing for organic brain deficit (various instruments) and personality changes (MMPI); a diagnosis of delirium was based on retrospective chart-review	13%
Sachdev+◆[13]	1967	10	5/5	47.8	31-68 years; selection of 'at risk patients'(?); single and multiple valve replacement	prospective; pre-OP: neurologic examination; post-OP: daily neurologic examination and psychologic interview+information staff	8/10=80% ?
Edington[14]	1968	27 (33)*	all ♂	45.5	24-60 years; aortic and mitral valve replacement, closure atrial septal defect	prospective; pre-and post-OP: semi-structured interview with patients and their relatives+information staff	6/27=22% (18%)*
Lazarus[15]	1968	1)21 2)33	? ?	? ?	≥16 years; consecutive excl. pts. who died within a month post-OP; open-heart surgery	prospective, controlled intervention study (1=intervention group=pre-OP supportive, psychiatric interview+specific recommendations for PO-care; 2= control group); post-OP recording of behavioural abnormalities by medical staff	1)14% vs. 2)33%

Delirium after cardiac surgery: a review of the literature (contd.)

author	year	no.of patients	♂/♀	mean age	selection	methods	incidence
McClish◆[14]	1968	79	28/51	±24	56 adults and 23 children; consecutive; open-heart surgery for aortic, mitral and congenital lesions; intervention (diazepam PO,n=42)- and controlgroup (n=37)	prospective; pre-OP+post-OP interview and behavioural assessment by an anaesthesiologist, directed at tracing 'minor&major psychiatric reactions' (3-4x/day during ± 1 week) incl.information staff	6% (major) 13%(minor)
Henrichs◆[17]	1969	43 (54)*	19/24 (24/30)	38.8	adults 16-61 years; consecutive; open-heart surgery for aortic, mitral and congenital lesions	prospective; pre-OP+post-OP (before discharge) psychological evaluation (MMPI)	?
Javid◆[18]	1969	100	?	46.9	>21 years; consecutive; aortic and mitral valve replacement, surgery for congenital and aneurysm lesions	prospective; pre-OP: standardized neurologic and mental status examination; post-OP: daily standardized neurologic and mental status examination+observation staff	35% behavioural disturbances
Kimball◆[19]	1969	54	21/33	45	18-72 years; consecutive in two periods; surgery for aortic valve, mitral valve and congenital lesions	prospective; pre-OP psychiatric interview directed at anxiety, life-style and orientation at the future; post-OP observation+chart-review+information of staff and relatives	n=9=16.6%
Morse[22]	1969	39	?	?	delirious group (n=20) vs. matched controlgroup (n=19); cardiac (open+closed) and great vessel surgery	retrospective case-control design; part of a larger PO study; post-OP psychiatric evaluation (checklist, regularly) incl. information staff+relatives	unknown for cardiac pts only
Rubinstein[21]	1969	36	15/21	?	20-69 years (most patients in age group 40-49 yrs); consecutive; cardiac surgery for aortic valve, mitral valve and congenital lesions	prospective; pre-OP psychiatric evaluation+standardized mental status examination; post-OP daily standardized mental status ex. incl. information staff (excl.pts. without a 'lucid interval')	31%
Heller[22]	1970	89 (100)*	?	50	>18 years; random selection; aortic and mitral valve replacement, mitral commissurotomy, congenital defect repair and miscellaneous	prospective; pre-OP: psychiatric interview+mental status examination+ psychometric examination (various tests); post-OP: daily psychiatric interview+chart review, day 2 PO psychologic tests, day 7 PO more extensive interview+scaling of psychopathologic findings	n=21=24% 9% PO-OBS^
Tufo[23]	1970	85 (100)*	50/50	?	31-65 years; consecutive; aortic- and mitral valve replacement and repair, surgery for congenital defects, aneurysm resection	prospective; pre-OP+post-OP standardized neurological and mental status examination (regularly) incl.psychometric examination pre-OP and before discharge	24-34-43% depending on severity# n=29=34%
Danilowitz[24]	1971	1)56 2)56	32/24	1)30.3 2)29.7	1)16-55 years old English-speaking versus 2) 15-59 years old non-English-speaking matched (for age, sex, type and severity of heart disease, date and type of operation) patients; cardiac surgery for congenital and valvular defects	both retrospective (6 yrs) as prospective (3 yrs); chart review and direct observation (?)	1) 3.9% 2)29.4%
Freyhan◆[25]	1971	121 (150)*	53/97	43	10-65 years; unselected sample of all patients undergoing open-heart surgery for miscellaneous lesions esp. valve lesions;	prospective; pre-OP: standardized psychiatric evaluation; post-OP: daily psychiatric interview+observations (PO psychopathological profile)	62% 51%)* psychiatric symptoms)
Layne[26]	1971	1)40 2)18 3)20	1)+2)= 34/247	1)+2)= 42	>14 years; consecutive; 1)experimental cardiac (pre-OP interview)group versus 2)control cardiac group versus 3) control vascular group; 1)+2)=surgery for aortic and mitral valve and congenital lesions, 3)= resection aneurysm aortae (n=19)+ coronary artery bypass graft (n=1)	prospective; pre-OP: group 1 extensive interview+standard questionnaire+ neurologic examination, group 2+3 neurologic examination; post-OP: daily mental status examination+ neurologic examination day 2 PO	1) 10% 2) 22% 3) 0% = 14%

Delirium after cardiac surgery: a review of the literature (contd.)

author	year	no.of patients	♂/♀	mean age	selection	methods	incidence
Lee◆[27]	1971	86	27/59	35	16-58 years; random selection; patients undergoing cardiac surgery with (experimental group, n=71) versus without (control group, n=24) extracorporeal circulation excl.IQ≤80	prospective; pre-OP: standardized neurological, psychiatric and psycho metric evaluation (different instruments); post-OP: idem as pre-OP day 10 and 3 months postoperatively	14%, all psychiatric complications tin exp.group
Morgan◆[28]	197	67 (72)*	36/36	?	7-70 years (8 pts<20 yrs, 40 pts between 41-60 yrs); cardiac surgery for aortic valve, mitral valve and congenital lesions	prospective; pre-OP: semi-structured interview focused on psychological attitude to operation; post-OP: daily mental status examination +observations medical staff	29.8% ? (23.6)* ?
Blacher◆[29]	1972	12	?	?	12 'post-operative normal' patients were selected by the nurses from a group of 300 pts. during a 9 month period for psychiatric evaluation; cardiac surgery	psychiatric interview	67% ? n=24=36% (31.5%)*
Kimball✡[30]	1972	66 (76)*	39/37	±45	21-69 years; consecutive; cardiac surgery for aortic valve, mitral valve and congenital lesions	prospective; pre-OP: psychological interview+a battery of tests for measuring anxiety, depression, dependency, coping adjustment and cognitive deficits; post-OP: daily 11-item behavioural rating on a 5-point scale	
Kornfeld[31]	1974	142 (153)*	?	?	≥18 years; random selection; aortic-, mitral- and multiple valve replacement, surgery for congenital defects, mitral commissurotomy	prospective; pre-OP: personality-, IQ- and organicity tests (n=87), standardized psychiatric interview (all); post-OP: psychiatric interview+ chart review (each day), organicity tests (day 2 post-OP), intensive psychiatric interview (day 7 post-OP)	n=35=25% after a lucid interval; 6% PO-OBS^
Quinlan✡◆[32]	1974	58 (76)*	43/33	45.3	20-69 years; consecutive; aortic- and mitral valve replacements, commissurotomies, coronary artery bypass grafts and miscellaneous procedures	prospective; pre-OP: semi-structured interview resulting in two factors: 'emotional stability' and 'level of anxiety'+test instruments, rating of organic brain dysfunction on 5-point scale; post-OP: daily 11-item behavioural checklist, rated on a 5- point severity scale	?
Surman[33]	1974	1)20 2)20	6/14 7/13	50.7 49.2	randomly assignment of elective mitral surgery patients to intervention (pre-OP psychiatric visit(s)) and control group	prospective, controlled study; pre-OP: psychiatric interview+ simple auto-hypnotic technique for experimental group; post-OP: mental status ex.for delirium, ratings for anxiety, depression and pain for exp.group; daily rating of both groups for delirium etc.based on observations of the nurses	n=11=27.5% 1)6/20 2)5/20
Kilpatrick◆[34]	1975	87	28/59	35	16-60 years; cardiac surgery (with -72 pts- versus without -15pts- extra-corporeal circulation)	prospective; pre-OP evaluation of cardiac impairment; intellectual, personality and neuropsychological function (various instruments); after 2 years all patients were designated survivor or fatality	?
Rabiner♣◆[35]	1975	1) 51 2) 46	45/6 25/21	54.8 55.0	consecutive; 1) coronary artery bypass versus 2) valve surgery	prospective; pre-OP: psychiatric interview; post-OP: daily mental status examination incl. 24-hours information of the staff; pre- and post-OP brief psychological test battery	1)16% 2)41% (psychiatric symptoms)
Sveinsson[36]	1975	95	82/18	64	13-80 years, only 19 pts.>60 years; consecutive; coronary artery bypass graft, valve replacement, commissurotomy and congenital defect repair	prospective; pre-OP: mental status evaluation+chart review; post-OP: daily mental status examination+information staff	n=6=6.3%
Willner♣◆[37]	1976	100	69/31	55.6	≥16 years; consecutive; coronary artery bypass (n=42), valve replacements (n=48), bypass+valve (n=6) and other procedures (n=4); excl. when psychiatric history; final sample 87 and 64 pts. respectively for 1) analysis of pre-OP CLAT- score and post-OP psychiatric symptoms 2) Surgical procedure and post-OP outcome	prospective; pre-OP: psychiatric interview+psychological tests incl. for cognitive function (a.o.CLAT); post-OP: mental status ex.incl. behavioural information from staff	±18% ?

Delirium after cardiac surgery: a review of the literature (contd.)

author	year	no.of patients	♂/♀	mean age	selection	methods	incidence
Merwin[39]	1977	30	28/2	52	40-71 years; consecutive; coronary artery bypass graft	prospective; pre-OP: structured interview with patient and his spouse; post-OP: daily mental status examination+information personnel and family	33%
Kornfeld[39]	1978	100	93/7	62.1	35-65 years; consecutive; coronary artery bypass surgery	prospective; pre-OP: standardized psychiatric interview, personality tests; post-OP: psychiatric interview+chart review (each day), intensive psychiatric evaluation (day 7 post-OP)	n=28=28% after a lucid interval; 1% PO-OBS^
Heller[42]	1979	1) 24 2) 24	18/6 7/17	60.8 54.2	1) 28-76 years; aortic valve replacement (+ coronary artery bypass) 2) 30-76 years; mitral valve replacement	retrospective, blind (for cardiac output) chart review for signs of delirium after a lucid interval, described by the medical staff	1) 46% 2) 29%
Sadler†[41]	1979	60	?	?	elective surgery; excl. pts. with preoperative psychiatric disturbances or other diseases	prospective; post-OP: assessment interview (+delirium assessment checklist) every evening of the first week PO	72% ? or 12% ?
Summers[42]	1979	27 (30)*	?	?	consecutive; cardiac surgery for coronary artery disease and valve lesions	prospective; pre-OP: standardized interview for psychiatric disturbances (Feigner criteria) and intellectual functioning; post-OP: at least 5x standardized interview+chart review	n=6=22%
Kolika◆[43]	1980	204	?	66	14-83 years; consecutive; 50% of the pts.underwent coronary artery bypass graft as the sole surgical procedure and ?; no pts. were excluded from the study	prospective; pre-OP: history, no evaluation ; post-OP: interview of most of the pts. and their family, 3-7 days following operation for neurologic and neuropsychological abnormalities, supplemented by chart review	37% ? esp. dis orientation or memory loss
Sadler†[44]	1981	60	?	64.1	28-72 years; excl. pts. with preoperative psychiatric disturbances or other diseases; aortic and mitral valve replacement, commissurotomy and ?	prospective; post-OP: assessment interview (+delirium assessment checklist) every evening of the first week PO	72% ? or n=6=12%
Tune[45]	1981	29	17/12	55	29-75 years; mitral valve replacement (n=15) and aortic valve surgery (n=14)	prospective; pre-OP: MMSE, perceptive function (with tachiscope) and reaction time; post-OP: mental state examination+pre-OP tests, 24 hours after surgery and 3 times a week for the next 2 weeks	n=10=34%
Morin[46]	1982	2811	?	54	coronary artery bypass, valve replacement, surgery for congenital defects, aneurysm resection	retrospective chart review for delirium according to DSM-III criteria	3%
Owens[47]	1982	1)32 2)32	?	54.1	≥18 years (21-74 yrs); consecutive; elective cardiac surgery (esp. coronary bypass and valve replacement) excl. pts. with a history of psychiatric or organic braindisease; 1) pre-OP intervention vs. 2) controls	prospective; random assignment to experimental (pre-OP education) or control group, pre-OP: standardized interview directed at eliciting evidence of cognitive or sensory disturbances; post-OP: interviews on day 4-8+ chart review	1)19/32 → 2)25/32 68% 'unusual experiences'
Slogoff◆[48]	1982	1)110 2) 94	100/10 78/16	55.0 54.6	adult pts. without neurologic or psychiatric illness; elective coronary artery or open ventricle cardiac surgery; 1) thiopental pre-OP vs. 2) controls	prospective; random assignment to group 1 or 2; pre-OP standardized neuropsychiatric evaluation; post-OP day 1,4 and 10 standardized neuropsychiatric evaluation+ trailmaking test day 4	13.2% psychiatric 'abnormalities'
Naber◆[49]	1985	23 (26)*	all ♂	54±12	consecutive; aortic valve replacement	prospective; pre-OP+post-OP (day 3,6,12): psychiatric ex.and standard behavioural ratings; pre-OP+post-OP(day 12): psychological questionnaires, measuring anxiety, stress appraisal and coping style (pre-OP)	13.0, 21.7% or 34.7% ?
Quintess[50]	1985	107	79/28	57.5	consecutive patients, excluding pts. with a psychiatric diagnosis, severe auditory/visual impairment, non-English speaking; elective cardiac surgery mostly for coronary artery bypass graft (80%)	prospective; pre-OP: interview and psychometric tests; post-OP: 11-item behavioural checklist by nurses during the first 2 days PO. A positive score on only one of the items evidently meant already 'some degree of psychosis'?	all patients n had some degree of psychosis ?

Delirium after cardiac surgery: a review of the literature (contd.)

author	year	no.of patients	♂/♀	mean age	selection	methods	incidence
Shaw◆[51]	1985	312	276/36	53.4	33-70 years; elective coronary artery bypass excl.: emergency surgery, stay on I.C.U. immediate before surgery, those admitted less than 24 hours before surgery and those who did not speak English	prospective; pre-OP: detailed clinical neurological+ neuropsychological (10 standard tests) assessment; post-OP: daily neurological assessment; day 7 PO repeat psychometric testing	1% PO-psychosis; 3% PO-OBS^
Nuss-meyer◆[52]	1986	1)89 2)93	60/29 64/29	57 55	1) thiopental peroperative- vs 2)control patients; elective, first-time open-heart surgery (valve replacement or repair, aneurysm resection, closure of septal defect excl. pts. with psychiatric or neurologic abnormalities or a history CVA or other neurologic disease	prospective; controls matched for sexe and age; pre-OP: standardized - neuropsychiatric evaluation; post-OP: standardized neuropsychiatric evaluation day 1 and 5	1) 5/89? 2) 4/93?
Calabrese[53]	1987	59	all ♂	58.5	40-75 years; consecutive; elective, first time-coronary artery bypass	prospective; pre-OP: psychiatric evaluation (SADS, HDRS, HARS, mental status); post-OP mental status examination; pre-OP+post-OP (day 6): neuropsychological assessment(several instruments)	n=4=6.8%; all pts delirious while on I.C.
Harrell◆[54]	1987	27	14/13	59.5	20-79 years; consecutive; valve replacement (n=3); coronary artery bypass (n=24)	prospective; pre-OP: medical and psychiatric questionnaire+MMSE; post-OP: daily MMSE+sleep parameters	?
Carella◆[55]	1988	87 (91)*	all ♂	54	53-69 years; consecutive, male patients; elective coronary artery bypass surgery	prospective; pre- and post-OP(day 8 PO): standardized neurological-, psychiatric- and psychometric evaluation (BPRS+several instruments)	n=3=3.4%
Edmunds◆[56]	1988	100	44/56	83.1	≥80 years (80-97 yrs); consecutive patients with advanced cardiac disease; excl. dementia and disabling non-cardiac problems, precluding an (semi) independent life;all surgery for aortic valve-, mitral valve- and/or coronary artery disease, aneurysm resection	unknown method; postoperative delirium is mentioned as a postoperative complication	12%
Folks◆[57]	1988	391	342/49 (17/5 study pts)	55	30-67 (study patients 46-65, mean age 60) years; coronary artery bypass surgery excl.: women of child-bearing age, a history of psychiatric disorder, sociopathy, cerebral infarct, dementia, substance abuse and age over 65	prospective, case (MMSE<20, n=25)-controlled (MMSE=30) design; pre-OP+post-OP (day 4) : standardized psychiatric interview (incl.self-report psychiatric instruments for depression, anxiety, psychosocial adjustment and cognition)	5.6% PO-OBS^ acc. DSM-III criteria

◆ = *study-outcome not (only) delirium*
^ = *PO-OBS = postoperative organic brain syndrome*
♣ = *(partly) same study population ?*
• = *(partly) same study population ?*
= *group 1: confusion+disorientation+delirium=24% (certain delirium)*
group 2: confusion+disorientation=10% (probable delirium)
group 3: confusion only=9% (possible delirium)
* = *postoperative deaths included*
✡ = *(partly) same study population ?*
‡ = *same study population*

Chapter 3

POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS IN THE OCCURRENCE OF DELIRIUM

Chapter 3.1

THE ROLE OF AMINOACIDS AND NEUROTRANSMITTERS: A REVIEW

INTRODUCTION

In general, delirium is considered a non-specific psychopathological manifestation of global cerebral dysfunction as a response to a variety of insults to the brain [1,2]. A large number of determinants and intervening pathophysiological mechanisms may result in a relatively circumscribed set of symptoms i.c. delirium [2]. In 1959, Engel and Romano were the first to describe delirium as a "syndrome of cerebral insufficiency" owing to a reduced cerebral metabolism [3]. Since then, delirium is generally viewed as a psychopathological and behavioural expression of widespread reduction of cerebral oxidative metabolism and imbalance of neurotransmission [2]. This may be due to a lack of oxygen, glucose or aminoacids, to a vitamin deficiency, to deficient synthesis, blockade or imbalance of certain neurotransmitters, to accumulation of toxins or false transmitters, to an altered cerebral blood flow, to an increased permeability of the blood-brain barrier, to hyper- and hypothermia and to damage to cell membranes; to name a few possible pathophysiological mechanisms [2]. Reduced level of consciousness, the key symptom of delirium as manifested by a disordered attention and arousal, is usually associated with diminished cerebral substrate supply and altered metabolic rate (CMR) and/or blood flow (CBF) in (certain areas of) the brain. CBF and substrate (oxygen, glucose or aminoacids) supplies may be adequate, yet CMR may be reduced and the level of consciousness lowered. In the latter case, a reduction in neuronal activity and a corresponding drop in energy demand are likely to occur [2]. On the whole, there is a coupling of neuronal activity, CMR and CBF. However, nothing is known about the precise pathophysiological processes by which delirium is mediated [2]. It seems quite probable that delirium involves more than one pathophysiological mechanism and that different, specific neuronal systems in the brain are important in the occurrence of (certain aspects, clinical subtypes or particular kinds of) delirium [1,2,4,5]. Although there is debate whether in delirium there is a more localized or widespread involvement of both cortical and subcortical structures, the few studies of cerebral metabolism in delirium are consistent with the idea of different forms of delirium, based on different pathophysiological processes and the disruption of specific neuronal systems [1,2,6].

The neurophysiological basis of the control of normal attention and arousal, uniquely disturbed in delirium, is still poorly understood and little is known about the changes occurring with aging, an important risk factor for delirium [2]. Knowledge about the involvement of the different brain neuronal systems in the proces of aging, especially those concerning attention and arousal, may clarify the underlying pathophysiological mechanisms in delirium.

ATTENTION, AROUSAL AND THE SLEEP-WAKE CYCLE

Impairment of attention and arousal, with hypo- or hyperalertness, is an invariably present, core feature of delirium, resulting in decreased concentration and distractibility [see chapter 1.2]. The normal functions of central arousal systems (the Ascending Reticular Activating System -ARAS-, generally viewed as extending from the thalamus, basal forebrain, hypothalamus and more

caudal brain stem to the cerebral, especially frontal and prefrontal cortex) are to regulate sleep and waking [1,2]. Research evidence indicates that the ARAS has many components such as the ascending noradrenergic, dopaminergic, serotoninergic and cholinergic systems, whose action seems to mediate different aspects of arousal, as well as attention and motivation [2]. Disorders of these different cortical afferent projections may relate to the pathophysiology of delirium [1]. The regulation of the sleep-wake cycle also involves various neuronal systems and a number of neurotransmitters: Cholinergic, serotoninergic and noradrenergic pathways appear to play an important interactive role in this.

Given the paucity of electrophysiological and neurochemical research in delirium and the complexity of the hypotheses on arousal, sleep and waking regulation, it is speculative to draw any conclusions about the relationship between the occurrence of delirium and abnormalities of these important functions. Besides, many data concerning the possible regulation-mechanisms of (higher) cerebral functions are derived from animal-research.

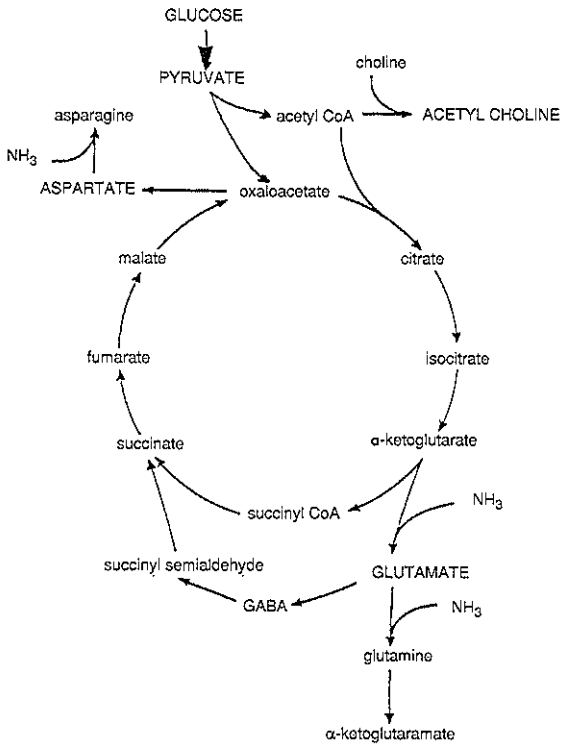
THE NEURONAL BASIS OF DELIRIUM

DELIRIUM AND CHOLINERGIC DYSFUNCTION

The central cholinergic system appears to be particularly vulnerable to all kinds of insults especially to diminished availability of either glucose or oxygen. It has been suggested that a reduced synthesis of acetylcholine is the final common pathway of delirium [5,6]. Since the synthesis of neurotransmitters consumes only small quantities of ATP, this is not necessarily due to a general impairment of energy production in the brain. In general, a more likely cause of neurotransmitter failure with disturbed brain metabolism is substrate deficiency [5]. The synthesis of cerebral acetylcholine is easily endangered since its precursor acetyl-coenzyme A is also an important, rate-limiting factor of the, oxygen and glucose demanding, aerobic citric acid cycle (figure 1). Although less than 1% of the glucose or pyruvate that is oxidized is incorporated into acetylcholine, carbohydrate catabolism, the synthesis of acetylcholine and oxidative processes in the central nervous system are closely linked (figure 1) [6]. Insulin-induced hypoglycaemia and nicotinic acid and thiamine deficiency have been shown to reduce the acetylcholine synthesis and transmission in the brain of animals, an effect that is (partially) reversible by administration of a central acting acetylcholinesterase inhibitor [5,6].

Hepatic encephalopathy (HE) may be partially caused by a reduced rate of acetylcholine synthesis due to the diversion of acetyl-coenzyme A into the citric acid cycle necessary for the increased conversion of alpha-ketoglutarate in glutamate and glutamine caused by the toxic levels of ammonia (figure 1) [5]. In this way the excess of ammonia in the brain also has a negative influence on the cerebral energy production by interfering with the energy producing citric

Figure 1
The citric acid cycle



acid cycle [7].

Evidence to date suggests that only a few neurotransmitters (the catecholamines, serotonin, acetylcholine, GABA, histamine and glycine) are subject to aminoacid precursor control [8]. Choline availability is a major factor in the synthesis of acetylcholine [8]. A decreased cerebral supply of choline, for example as a consequence of diminished precursor availability of fosfatidylcholine and/or the methyl donors methionine and serine, or reduced incorporation of choline into acetylcholine due to hypoxia and hypoglycaemia affects acetylcholine synthesis [6]. The changes in acetylcholine synthesis as a consequence of the aforementioned mechanisms occur without alterations in the levels of cerebral acetylcholine, indicating that diminished release of acetylcholine underlies the reduction in formation and neurotransmission [6].

Furthermore, experimentally as well as clinically, anticholinergic agents that can cross the blood-brain barrier, appear to be strongly deliriogenic, indicating that the disturbance of the central cholinergic neurotransmission plays an important role in the occurrence of (certain specific kinds of) delirium [1,2,5,6,9]. Elderly patients and patients with dementia of the Alzheimer's type are especially prone to this deliriogenic effect, because of their already

less functional cholinergic system [5,6]. A positive association has been found of anticholinergic activity in serum, plasma (and CSF in patients with spinal anaesthesia) with (postoperative) cognitive impairment and delirium [9,10, 11]. Delirium associated with anticholinergic agents can be reversed by the anticholinesterase inhibitor physostigmine [1,2,5,6].
The central cholinergic system is widespread distributed throughout the brain and known to be involved in the regulation of arousal, attention, memory processes and REM-sleep, all functions disordered in delirium [1,2,5,6]. Thus, a decreased acetylcholine synthesis and cholinergic neurotransmission due to 1. substrate deficiency (glucose, oxygen, acetyl-coenzyme A and choline), 2. a blockade of the cholinergic transmission by anticholinergic agents and 3. a relative impairment of the cholinergic system as a result of the overactivity of other neurotransmitter systems, are probably important contributors to the occurrence of (some types of) delirium, especially in elderly subjects and in patients with dementia.

DELIRIUM AND MONOAMINERGIC DYSFUNCTION

Like the cholinergic system, the monoaminergic systems (consisting of the catecholamines: dopamine, adrenaline and noradrenaline and the indolamine: serotonin) are supposed to be involved in the control of the sleep-wake cycle and the maintenance of arousal. Most probably, the two systems interact, with the cholinergic mechanism increasing attention while selectively inhibiting the more automatic motivational and affective responses to stimuli mediated by the monoaminergic arousal system [5]. Besides, the cerebral serotoninergic neurons projecting from the midbrain raphe nuclei of the brainstem to widespread areas of the cerebral cortex, are involved in functions such as (the control of) aggressive and impulsive behaviour, anxiety, mood and motor activity and may well play some role in the pathophysiology of (the hyperalert-hyperactive type of) delirium [1]. Raphe neurons show prominent changes with behavioural activity: most active in wakefulness, less active in slow-wave sleep and least active in REM sleep, an effect more linked to muscle activity than to the actual state of arousal.
An increased dopaminergic release and transmission is known to cause psychotic disturbances and the effectiveness of antipsychotic medications in treating the hallucinations and delusions, frequently seen in delirium suggests that this system also may be involved in the pathophysiology of these symptoms of delirium [1].
The (nor)adrenergic neurons projecting from the locus coeruleus to widespread areas of the cerebral cortex show striking alterations in discharge rates with the state of arousal: highest in wakefulness, less during slow-wave sleep and near silence during REM sleep [1]. However, the locus coeruleus does not seem to play an important role in the normal regulation of the sleep-wake cycle, but more in the modulation of attention [1]. Furthermore, the noradrenergic system is important in mood and anxiety regulation.

Also, the cholinergic system is not the only cerebral neurotransmitter system

sensitive to all kinds of insults. The synthesis of catecholamines and indoleamines is vulnerable to a deficiency of oxygen and precursors as well [5,6]. The rate-limiting step in the synthesis of the monoamines dopamine, noradrenaline and serotonin, as well as their degradation, require oxygen [6]. The significance of inhibition in synthesis is controversial, since during stress the dependence of amine synthesis on oxygen availability is abolished [6]. Contrary to the inhibiting effect on the release of acetylcholine, hypoxia does not alter, both in vitro and in vivo, the release of noradrenaline or serotonin and increases extracellular dopamine [1]. This change in extracellular dopamine may contribute to cell death and also to the behavioural changes that accompany delirium [6].

Dysfunction of cerebral monoaminergic systems, especially the serotoninergic, may, next to an increased synthesis of glutamine and dysfunction of the cholinergic system, contribute to HE (figure 1). In liver disease there is an increase in the aminoacids tyrosine and tryptophan (the precursors of the catecholamines and serotonin, respectively), as a consequence of impaired hepatic oxidative deamination. Contrary to the synthesis of dopamine and (nor)adrenaline from its precursor tyrosine, the rate of synthesis of cerebral serotonin is directly affected by changes in the plasma level of its precursor tryptophan (TRP) [5,8]. In addition, the excess of glutamine (via increased ammonia) in the brain may stimulate the cerebral TRP-uptake and by this the synthesis, release and function of serotonin [7,13]. The increased activity of cerebral serotonin may be partly responsible for the clinical picture of HE, which resembles the so-called "serotonin syndrome", described in patients using a Selective Serotonin Re-uptake Inhibitor or TRP and Mono Amine Oxidase-Inhibitors at the same time, being characterized by psychiatric symptoms as confusion, hypomania and agitation and neurological symptoms as clonus, hyperreflexia, inco-ordination, increased transpiration, tremors and also diarrhoea and fever [7,12,13]. In HE, the increased production of other metabolites of TRP like tryptamine, quinolinic acid and substances like tyramine and octopamine may be a source of false neurotransmitters, interfering with normal neurotransmission [5,7]. However, the role of false neurotransmitters in HE has to be established.

Alcohol withdrawal delirium is another form of delirium associated with monaminergic dysfunction, in particular of noradrenaline [2]. The levels of noradrenaline and its major metabolite, 3-methoxy-4-hydroxy-phenylglycol (MHPG) are elevated in the alcohol withdrawal syndrome. Repeated withdrawals may lead to so-called "kindling" and successively enhance noradrenergic overactivity [2]. In any way, symptoms of alcohol withdrawal (delirium) are more likely due to rebound hyperexcitability of the CNS and chronic changes in neuronal receptor populations (supersensitivity) rather than to acute metabolic disturbances [5]. For example, alcohol withdrawal has been shown to be associated with increased central beta-adrenergic receptor sensitivity [5]. It is possible that this enhanced noradrenergic activity under-

lies some of the core characteristics of the alcohol withdrawal delirium, such as hyperalertness, hyperactivity and overactivity of the sympathetic nervous system [2]. EEG changes in alcohol withdrawal delirium are different from those found in delirium due to other causes, suggesting different pathophysiological mechanisms [2].

TRP metabolism, cerebral availability and thus central serotoninergic function in man are likewise shown to be influenced by acute and chronic alcohol consumption and subsequent withdrawal [14]. The findings to date are contradictory, but chronic alcoholics appear to have decreased plasma TRP concentrations and ratios of TRP to the other competitive amino acids (although also decreased), possibly due to nutritional deficiencies. However, these abnormalities in TRP metabolism may also be of a metabolic (alcohol enhances hepatic TRP pyrrolase activity in the absence of any increases in concentrations of circulating cortisol and TRP) or genetic nature [14]. In rats, alcohol withdrawal has been shown to cause an enhancement of liver TRP pyrrolase activity leading to a decrease in the availability of circulating TRP to the brain with a consequent inhibition of cerebral serotonin synthesis. This pyrrolase enhancement during withdrawal appears to be of the hormonal type, which is suggested by the observed correlation with the elevation of circulating corticosterone concentration [14].
Summarizing, one could hypothesize that alcohol withdrawal (delirium) may be the result of a strongly imbalanced neurotransmission in the brain, caused by overactivity of the noradrenergic system due to elevated levels of cerebral noradrenaline in combination with supersensitivity of the alpha-adrenergic receptors and to decreased function of the serotoninergic system owing to the generally reduced cerebral TRP availability in chronic alcoholics, even more aggravated by the glucocorticoid mediated enhancement of the hepatic TRP pyrrolase under these stressful circumstances [15]. Besides, these changes in adrenergic and serotoninergic activity in the brain very probably influence the function of the other neurotransmitter systems as well.

In humans, chronic levodopa treatment may give rise to serious sleep and psychotic disturbances and even delirium, related to the dose and duration of levodopa therapy and possibly associated with concurrent cerebral atrophy [2,16]. Nausieda et al. [16] concluded that fragmentation of the sleep-wake cycle and sleep architecture, as well as altered dreaming precede the development of the psychiatric symptoms. They postulate that these symptoms may, next to increased mesolimbic dopaminergic activity, also be due to changes in serotoninergic function, since levodopa reduces plasma and brain levels of TRP by competing with TRP for uptake from the gut and at the blood-brain barrier. This would initially reduce central serotonin levels (decreased activity), later on, through chronic shortage of TRP, followed by sensitization of the serotonin receptors (increased activity) [2,16]. The inconclusive results of L-TRP treatment and 5-hydroxytryptophan in patients exhibiting psychiatric symptoms while receiving levodopa may be explained by different stages of

the disease (with a different degree of intellectual impairment) and the treatment duration with levodopa [17].

DELIRIUM AND DYSFUNCTION OF OTHER CENTRAL NEUROTRANSMITTERS

Only a small proportion of the neurons in the brain are cholinergic or monoaminergic and it is possible that impairment in the function of other neurotransmitter systems also contribute to the clinical picture of delirium [5]. In fact, the most prevalent neurotransmitters in the brain are gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter and glutamate, a major excitatory neurotransmitter, both intimately involved with the energy producing citric acid cycle (figure 1). Therefore, like the cholinergic and monoaminergic systems, they are vulnerable to metabolic disturbances.

An increased cerebral GABA activity has been associated with the hypoalert-hypoactive clinical picture of HE [1,5,7]. The GABA receptor is a postsynaptic receptor complex with separate receptors for GABA, benzodiazepines and barbiturates [7]. By increasing the GABA receptor binding, benzodiazepines enhance GABA activity. GABA is produced by the gut flora, but is normally prevented from reaching the brain by liver metabolism and the blood-brain barrier [5,7]. In liver failure GABA enters the systemic circulation and, because of the possibly increased blood-brain barrier permeability, may result in an increased cerebral GABA-ergic neuronal inhibition, probably giving rise to the hypoalertness and hypoactivity seen in HE [5,7]. However, in patients with HE, normal concentrations GABA in liquor cerebrospinalis and post mortem brain tissue have been found as well as a normal number of GABA-benzodiazepine-receptor complexes, so it remains uncertain whether the GABA-ergic system is of importance in causing HE [7]. Withdrawal of benzodiazepines, sometimes causing a delirious syndrome of the hyperalert-hyperactive type, has been associated with a transient decrease of GABA inhibitory function [5].

The synthesis of glutamate, a glucose-derived aminoacid, is altered in anaemic hypoxia, hypoxic hypoxia and thiamine deficiency. Possibly, an excess of glutamate (like an excess of dopamine) can be implicated in cellular damage and some features of delirium [6].

Histamine also seems to be an important neurotransmitter in normal arousal, as demonstrated by the sedative effects of antihistamines [1]. The relevance of disturbances in histamine function to delirium is to date unknown.

Other substances reported in the literature to be possibly associated with the occurrence of delirium are beta-endorphin (an endogenous opiate peptide) and cortisol. Cortisol, an important (TSH-release-inhibiting) hormone that can account for changes in behaviour and cognition, has modulating effects on both the limbic system of the brain and the immune system [18]. In one preliminary study plasma beta-endorphins and cortisol were increased in three

postoperative delirious patients compared with four non-delirious patients, correlating with the length of the surgical procedure [19]. Moreover, normal plasma circadian rhythms of both beta-endorphin and cortisol were completely abolished in the delirious patients during the 48-72 hour postoperative period in which the patients became delirious [19]. This finding was not confirmed in another study, concerning 23 patients (of whom 8 became delirious) undergoing aortic valve replacement [20]. It may be that beta-endorphin dysfunction increases susceptibility to delirium, but the evidence to date is sparse and inconsistent [19-22]. Koponen et al. found a significant reduction in cerebrospinal fluid beta-endorphin-like and somatostatin-like immunoreactivity (with a declining trend associated with increasing cognitive dysfunction, as measured with the Mini Mental State Examination, a screening test for cognitive dysfunction) in respectively 69 and 67 elderly delirious patients compared with 19 non-delirious controls of the same age [21,22,24,25]. However, a major flaw of this study is that the delirious patients were recruited from new admissions to a psychogeriatric ward of a psychiatric hospital, most patients having premorbid structural brain disease (Alzheimer's disease, Multi Infarct dementia and Parkinson's disease), in contrast with the cognitive intact control patients [21-25]. The authors themselves finally conclude that dysfunction in beta-endorphin and somatostatinergic neurons is a common feature in at least more severe cognitive disturbances, but very probably play only a minor role in the pathophysiology of some symptoms of delirium, since there were no differences in the beta-endorphin and somatostatin levels between recovered and still delirious patients during follow-up [21]. These reductions in beta-endorphin and somatostatin levels probably reflect degeneration of the concerning neurons already before the onset of delirium, due to degenerative diseases of the brain [22-25].

Another substance that may be involved in the pathogenesis of delirium is the endogenous pyrogen interleukin-1 (IL-1), which is released from cells following a wide range of infectious, inflammatory and toxic insults [5,26]. IL-1 is involved in CNS functions as thermogenesis, induction of slow-wave sleep and release of pituitary hormones like corticosteroids [19,26]. The use of lymphokines like interferon, IL-2 and lymphokine-activated killer cells is associated with a dose-dependent development of cognitive and behavioural changes, including delirium, possibly caused by changes in neurotransmitter levels of noradrenaline and serotonin in the brain [19,26].

DELIRIUM AND THE ROLE OF SECOND MESSENGER SYSTEMS

Since multiple neurotransmitter systems may be affected by the different etiologies in a variety of ways, perhaps more fundamental processes in the neuronal cells are disturbed i.c. the second messenger system [6,27]. The second messengers (calcium, the phosphatidylinositol (PI) cascade and the cyclic nucleotides AMP and GMP) are signal transduction systems of importance in the synthesis and release of neurotransmitters. The signals relayed by the neurotransmitters are translated into cell function postsynaptically by second mes-

senger systems. Thus, alterations in second messengers may either reflect direct action on the cell or changes that are secondary to the alterations in neurotransmitter release [6,27]. For instance, experimental research on brain slices has shown interrelated alterations in calcium, cyclic AMP and GMP and the PI cascade under hypoxic circumstances [6].

NEUROPHYSIOLOGY OF AGING

Elderly persons are especially prone to develop delirium and age over 60 years appears to be a main risk factor for delirium. Despite the fact that the pathogenesis of delirium in elderly does not seem to be different, age-related changes in the brain, in particular in stress regulating and neurotransmitter systems and second messengers very likely play a major role in the higher incidence of delirium in elderly [1,2,6]. The cholinergic system is altered by aging through selective cell loss. The decline in synthesis and release of acetylcholine parallels the decrease seen in hypoxia and ischemia [6]. Deterioration of cholinergic function is thought to be related to the cognitive decline associated with it [2,6]. In aging, there is also some loss of midbrain dopamine neurons with relative preservation of postsynaptic receptors. However, the basal release of dopamine and glutamate, two neurotransmitters associated with cellular damage, in vivo is increased [1,6]. The noradrenergic locus coeruleus shows selective cell loss as a result of the aging processes and alterations in cortical serotonin(receptors) have been described [1,2].

Also, excessive (and reduced) levels of plasma cortisol have been associated with cognitive impairment and delirium in old age, together with 'an age-linked weakness of the stress-resisting mechanisms' in the brainstem and hypothalamus [2,5].

The precise significance of the above described cerebral changes for the pathophysiology of delirium in elderly is still unclear. However, in (experimental) animal research, aging seems to predispose the brain to the effects of hypoxia and thiamine deficiency on the neurotransmitter systems. Whether this is due to additive effects on second messenger systems is unknown, but aging and hypoxia also affect calcium homeostasis in a similar way, thus these additive effects may be the result of alterations in calcium homeostasis [6].

CONCLUSIONS

Hypotheses about the pathophysiology of delirium are speculative and largely based on animal research. Abnormalities of a number of neurotransmitters may be involved in different aspects (arousal and alertness, attention, memory etc.), clinical presentations (hyper- or hypoalert, hyper- or hypoactive, with hallucinations/delusions or not) and specific disorder-related forms of delirium (anticholinergic delirium, hepatic encephalopathy, alcohol and benzodiazepine withdrawal delirium, postoperative delirium etc.). In particular, (animal) research has been done on the effects of hypoxia, ischemia and thiamine deficiency on the synthesis and release of acetylcholine, noradrenaline, serotonin, dopamine, GABA and glutamate. The results from both animal- and human studies indicate that deficits in the cholinergic system may under-

lie some of the symptoms of delirium. However, the changes in the other neurotransmitters very probably also play an important role, an excess of glutamate and dopamine being held responsible for cellular damage and the psychotic features of delirium. Both an excess and a deficit of cerebral serotoninergic function, due to altered plasma concentrations and therefore cerebral availability of its precursor TRP have been associated with delirium. Furthermore, overactivity of the noradrenergic system, possibly due to elevated levels of cerebral noradrenaline and supersensitivity of the alpha-adrenergic receptors may be related to specific forms of delirium, for example (alcohol) withdrawal delirium.

Moreover, all these neurotransmitter (=first messengers) alterations probably have an additive effect on dysfunction of the intracellular signal transducing system, i.c. the second and third messengers, by this influencing again neurotransmitter synthesis and release. Furthermore, age-related changes in the brain may underlie the increased sensitivity of older patients to the development of delirium. However, despite the enormous progress made in the study of the brain during the last decades, it is so extraordinary complex that the precise mechanisms by which it (mal)functions yet remains largely unknown.

REFERENCES

1. Ross CA. CNS arousal systems: Possible role in delirium. In: Miller NE, Lipowski ZJ (eds). Delirium. Advances in research and clinical practice. International Psychogeriatrics 1991; 3: 353-371.
2. Lipowski ZJ. Delirium: Acute Confusional States. New York: Oxford University Press, 1990.
3. Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. J Chronic Dis 1959; 9: 260-277.
4. Ross CA, Peyser CE, Shapiro I, Folstein MF. Delirium: Phenomenologic and etiologic subtypes. In: Miller NE, Lipowski ZJ (eds). Delirium: Advances in research and clinical practice. International Psychogeriatrics 1991; 3: 135-149.
5. Lindesay J, Macdonald A, Starke I. The neuronal basis of delirium. In: Delirium in the elderly. Oxford, Oxford University Press, 1990: 66-79.
6. Gibson GE, Blass JP, Huang HM, Freeman GB. The cellular basis of delirium and its relevance to age-related disorders including Alzheimer's Disease. In: International Psychogeriatrics 1991; 3: 373-395.
7. Aaldijk C, Broek WW van den, Mast RC van der. The role of tryptophan in hepatic encephalopathy (in Dutch). Acta Neuropsychiatrica 1993; 5: 71-75.
8. Acworth IN, Wurtman RJ. Precursor control of catecholamine metabolism. In: Amino acids in psychiatric disease. Richardson MA (Ed.). American Psychiatric Press, Washington, D.C. 1990.
9. Tune LE, Damlouji NF, Holland A, et al: Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981; 2: 651-653.
10. Miller PS, Richardson JS, Christopher AJ, Lemay JS, Hiscock M, Keegan DL. Assocation of low serum anticholinergic levels and cognitive impairment in elderly presurgical patients. Am J Psychiatry 1988; 145: 342-345.
11. Golinger RC, Peet T, Tune LE. Assocation of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatry 1987; 144: 1218-1220.
12. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991; 148: 705-713.
13. Young SN. Factors influencing the therapeutic effect of tryptophan in affective disorders, sleep, aggression and pain. In: Amino acids in psychiatric disease. Richardson MA (Ed.). American Psychiatric Press, Washington, D.C. 1990.
14. Badawy AA-B. Effects of alcohol on tryptophan metabolism. Biochem Soc Trans 1988; 16: 254-256.
15. Buydens-Branchey L, Branchey M, Worner TD, Zucker D, Aramsombatdee E, Lieber CS.

Increase in tryptophan oxygenase activity in alcoholic patients. Alcoholism: Clinicaland Experimental Research 1988; 12: 163-167.
16. Nausieda PA, Weiner WJ, Kaplan LR, Weber S, Klawans HL. Sleep disruption in the course of chronic levodopa therapy: An early feature of the levodopa psychosis. Clinical Neuropharmacology 1982; 5: 183-194.
17. Beasly BL, Nutt JG, Davenport RW, Chase TN. Treatment with tryptophan of levodopa-associated psychiatric disturbances. Arch Neurol 1980; 37: 155-156.
18. Camara EG, Danao TC. The brain and the immune system: A psychosomatic network. Psychosomatics 1989; 30: 140-146.
19. McIntosh TK, Bush HL, Yeston NS et al. Beta-endorphin, cortisol and postoperative delirium: A preliminary report. Psychoneuroendocrinology 1985; 10: 303-313.
20. Naber D, Bullinger M. Neuroendocrine and psychological variables relating to post-operative psychosis after open-heart surgery. Psychoneuroendocrinology 1985; 10: 315-324.
21. Koponen H, Riekkinen PJ. A longitudinal study of cerebrospinal fluid beta-endorphin-like immunoreactivity in delirium: Changes at the acute stage and at one-year follow-up. Acta Psychiatr Scand 1990; 82: 323-326.
22. Koponen H, Stenback U, Mattila E, Reinikainen K, Soininen H, Riekkinen PJ. CSF beta-endorphin-like immunoreactivity in delirium. Biol Psychiatry 1989; 25: 938-944.
23. Koponen H, Stenback U, Mattila E, Soininen H, Reinikainen K, Riekkinen PJ. Delirium among elderly persons admitted to a psychiatric hospital: Clinical course during the acute stage and one-year follow-up. Acta Psychiatr Scand 1989; 79: 579-585.
24. Koponen H, Stenback U, Mattila E, Reinikainen K, Soininen H, Riekkinen PJ. Cerebrospinal fluid somatostatin in delirium. Psychological Medicine 1989; 19: 605-609.
25. Koponen H, Reinikainen K, Riekkinen PJ. Cerebrospinal fluid somatostatin in delirium. II Changes at the acute stage and at one year follow-up. Psychological Medicine 1990; 20: 501-505.
26. Kooiman CG. Psychoneuroimmunology and psychiatry; a literature review. (In Dutch). Tijdschrift voor Psychiatrie 1992; 34: 18-29.
27. Hyman SE, Nestler EJ. The molecular foundations of psychiatry. Washington, DC, American Psychiatric Press, 1993.

Chapter 3.2

CARDIOPULMONARY BYPASS, CATABOLIC STATE AND THYROID HORMONE METABOLISM: THE LOW T_3 SYNDROME

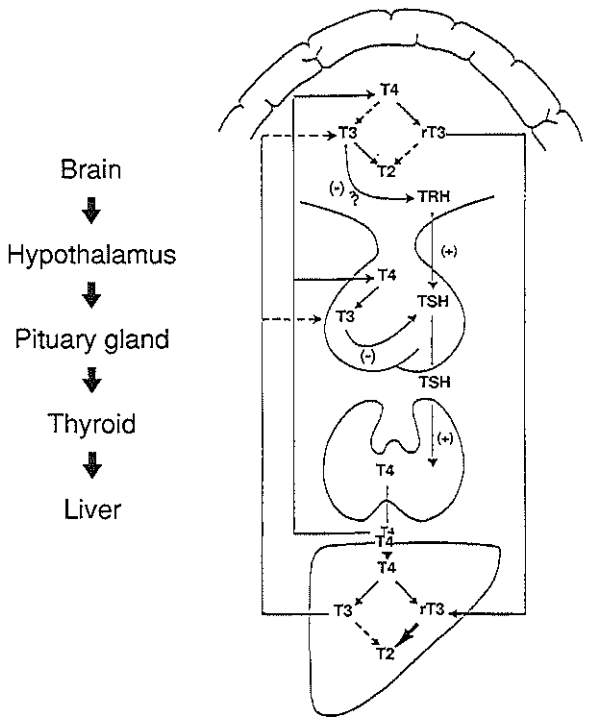
INTRODUCTION

To study the influence of a catabolic state on plasma concentrations of amino-acids and the occurrence of delirium after cardiac surgery with cardiopulmonary bypass (CPB) and hypothermia, a measure for severity of physiological stress c.q. catabolic state was needed, for which, next to the levels of cortisol and (pre)albumin, the ratio of reverse T_3:T_3 was chosen.

It has long been recognized that changes in thyroid hormone metabolism, leading to alterations in thyroid hormone serum parameters, accompany various physiological stressful events of sufficient intensity such as a wide variety of unrelated, non-thyroidal diseases and catabolic conditions like systemic illness, starvation and accidental or surgical trauma [1-6]. It appears that severe illness of any type predictably leads to abnormal results on thyroid function tests, the degree of alteration depending on the severity rather than on the type of illness [1-6].

The most frequent change is a reduction in the total active thyroid hormone: 3,5,3'-triiodothyronine (T_3), occurring within 24 hours after onset of illness. The lowered serum T_3 is often, but not always, accompanied by elevated levels of 3,3',5'-triiodothyronine (reverse T_3, rT_3), an inactive metabolite of thyroxine. The changes in serum T_4 are more complex, depending on the extent

Figure 1
Regulation of thyroid hormone metabolism



of fasting and the severity of illness [1-5]. In critically ill patients serum T_4 is often low, correlating with the probability that the patient will die [1-5]. Although the concentrations of thyroid-stimulating hormone may remain normal, they are often also affected [1-5].
These alterations in serum thyroid hormone parameters have been referred to as the 'euthyroid sick syndrome', 'low T_3 syndrome' or 'non-thyroidal illness' (NTI) [1-5]. The decrease in T_3 production in the liver may be regulated via various mechanisms: a.o. diminished availability of T_3 and T_4 caused by inhibited transport across the liver cell membrane into the cell, together with decreased conversion of T_4 into T_3 due to an impaired intracellular metabolism (figure 1) [3-6], both decreased transport and metabolism presumably being caused by depletion of ATP [4,6], and must be considered in relation with other coping-mechanisms of the body, facing life-threatening circumstances.

It is unknown whether the alterations in thyroid hormone metabolism that accompany various stressful and catabolic conditions are a beneficial or an adverse response and, if the latter, whether the apparent decrease in the availability of T_3 should be corrected with replacement therapy [1,3]. To date, the diminished availability of the active thyroid hormone is generally viewed as an adaptive mechanism to stressful circumstances, causing a decline in energy expenditure, supporting the healing process and the fight against the detrimental consequences of the underlying disorder [1,5].

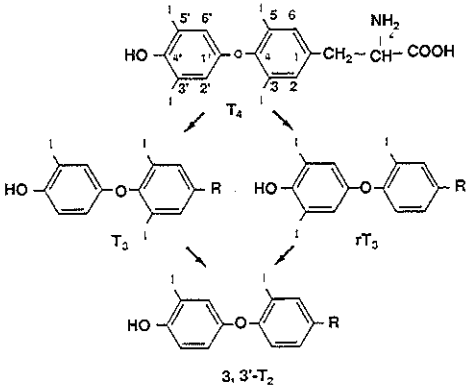
THYROID HORMONE METABOLISM

T_4, a predominantly inactive prohormone, is the main secretory product of the normal thyroid [7]. The major pathway of the T_4 metabolism is initially via deiodination (by the enzyme deiodinase) in the outer ring, producing T_3, the biologically active hormone; or in the inner ring, producing rT_3, a biologically inactive metabolite (see figure 2) [3,5,7]. Less than 20% of total T_3 is produced in the thyroid. The remaining 80-90% is being formed in the peripheral tissues, especially in the liver, being the central organ in the metabolism of T_4 and the kidneys and muscles [3,7,9]. Several tissues do not depend only on circulating T_3, but also to varying degrees on T_3 locally derived from T_4 [7].

Almost all of rT_3 in the plasma comes from inner ring monodeiodination of T4 in the brain, since in the liver rT_3 is produced and metabolised so rapidly, that it does not enter the circulation [7]. Both T_3 and rT_3 are deiodinated further to the diiodothyronines (T_2) and then to monoiodothyronines, all of them inactive metabolites, which are cleared rapidly from the plasma (figure 2) [5]. Iodothyronines in the circulation are predominantly bound to serum proteins, the biological activity being determined by the free hormone concentration [3,5,7].

The transport of thyroid hormones across the cell membrane is an energy (ATP)-dependent process [3,5-7]. The entry of iodothyronines into hepatocytes

Figure 2
Stepwise deiodination of T_4 via T_3 or rT_3 to T_2



is facilitated by albumin, but hampered by the presence of 'plasma inhibitors' [3,7-9]. These plasma inhibitors are found especially in patients with NTI, possibly as a consequence of tissue damage, but also in fasting conditions [8]. They also interfere with the binding of thyroid hormone to serum proteins [3,5,7-9]. Recently, four circulating inhibitors of T4 transport into rat hepatocytes have been identified: 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) and indoxyl sulphate in uraemia, and bilirubin and non-esterified fatty acids (NEFA) in critically ill patients with hyperbilirubinaemia [8]. In patients with mild illness these factors are not responsible for the inhibition of T_4 tissue uptake. The high concentration of NEFA during calorie restriction (fasting) actually appears to inhibit T_4 tissue uptake [8].

T_3 is transported via the circulation to the various tissues, where it has at least three receptor sites: 1. in the nucleus of the cell with an effect on gene expression, 2. a direct effect on membrane processes, leading to an enhanced transport of aminoacids and sugars and 3. a direct action on mitochondria to increase ATP synthesis [7].

The function of the thyroid is controlled by thyroid-stimulating hormone (TSH) from the pituary gland, which in turn is regulated by stimulating thyrotropin-releasing hormone (TRH) from the hypothalamus, the (negative) feedback of thyroid hormones on the production of TSH being an important regulating mechanism (figure 1). The production of TSH appears to be inhibited, among others, by dopamine (agonists), somatostatin and cortisol. The precise significance of this inhibition in relation to the stimulating action of TRH is not known [2,5].

In summary, the production and effects of T_4 and T_3 are regulated by a negative feedback on the production of TSH, by the plasma-availability of iodine to the thyroid (autoregulation), by the balance between T_3 and rT_3 production from T_4 in the liver and by the thyroid hormone binding to thyroxine-binding proteins e.g. thyroxine-binding globulin (TBG) [3,5].

THE LOW T_3 SYNDROME

The low T_3 syndrome, also called 'sick euthyroid syndrome' or 'non-thyroidal illness', means the presence of an illness together with an adequate thyroid function, but various erratic thyroid function tests [1-5,7]. As mentioned before, it is characterized by a decrease in the serum T_3 concentration, an increase in the rT_3 concentration, a normal or possibly lowered TSH concentration and a normal, increased or decreased T_4 concentration, depending on the severity of the stressful condition [1-5,7,9,10]. The diminished metabolism of T_4, resulting in a decline of T_3 can be explained by a decreased uptake or breakdown of T_4 by the liver [1-5,7]. The concomitant rT_3 increase is not so much a reflection of increased production as of a markedly reduced metabolic clearance rate of rT_3, due to reduced liver uptake and decreased enzyme activity.

An abnormal rT_3 level, in combination with a normal serum TSH level may distinguish patients with a non-thyroidal illness from hypothyroid patients. However, only a normal TSH response to TRH administration excludes the (co)existence of hyperthyroidism [2,3,7]. The more severe the illness, in terms of a higher mortality, days of admission and the extent of (surgical) injury, the lower the serum T_3, the higher the serum rT_3 and, finally, the lower the serum T_4 [1-5,7,9,10]. The following conditions are associated with a low T_3 syndrome: acute and chronic starvation especially the reduced intake of carbohydrates, chronic liver and renal disease, febrile illnesses of all kind, acute myocardial infarction, acute respiratory failure, uncontrolled diabetes and diabetic ketoacidosis, anaesthesia, accidental and surgical trauma, malignancies, acute and chronic systemic illnesses and many compounds and medications [1-4]. Since several studies reveal a clear decline in the serum T_3 level from middle through old age, aging itself is regularly considered a cause of the low T_3 syndrome [3]. As it turns out, this effect is most probably due to a lesser health and a more significant use of medications in an elderly population [2-4]. The evaluation of thyroid function in elderly sick patients becomes extremely difficult if not impossible when they are also using many different medications [2,4].

Thus, any physiological stress c.q catabolic state is accompanied by a low T_3 syndrome e.g. a decrease of T_3 and an increase of rT_3 , resulting in an increase of the rT_3/T_3-ratio, which can be considered as a measure for the extent of physiological stress and generally is viewed as a useful adjustment to illness in order to minimize the catabolic state and conserve energy [7].

CARDIOPULMONARY BYPASS AND THYROID FUNCTION

Thyroid hormone alterations are common following major surgery. Cardiac surgery e.g the hypothermia, non-pulsatile flow and hemodilution during cardiopulmonary bypass (CPB) is a form of trauma, that elicits cellular and humoral responses typical of generalized inflammation, which have major (endocrine) consequences like an increase in the dopamine release and the adrenal secretion of cortisol and serious alterations in the levels of rT_3, T_3, (TSH) and T_4 [9,11-13].

Zaloga et al. [9] longitudinally studied thyroid hormone serum concentrations in 59 patients aged between 31 and 69 years, undergoing coronary artery bypass grafting (n=54), pneumectomy (n=2) and colectomy (n=3). Within 6 hours of surgery changes in thyroid functions were seen. Initially, both the T_3 and the rT_3 decreased, followed by an increase in rT_3 and further decrease of T_3. Thus, an increase of the rT_3/T_3-ratio appeared already shortly after surgery. These changes normalized by 1 week after surgery. The mean plasma concentrations dopamine, measured in eight cardiac patients also changed significantly after surgery, the per cent increase of dopamine correlating with the per cent decrease in the serum TSH response to TRH, in accordance with the idea that elevated dopamine levels, like glucocorticoids, opiates, somatostatin and prostaglandins, suppress the hypothalamic-pituary axis [9].

Robuschi et al. [11] studied 32 patients between 38 and 71 years of age (average 52.9 ± 5.7), subjected to CPB (coronary artery bypass grafting and/or valve replacement). A marked decrease in serum total T_3 occurred already during induction of anaesthesia, only to decrease further with the start of CPB and hypothermia. The total T_3 remained significantly lower 2 and 12 hours after CPB. The rT_3 increased during anaesthesia, but declined after the start of the CPB and hypothermia. However, 2 and 12 hours after CPB there appeared to be a significant increase in serum rT3 concentration as compared to baseline, lowering the rT_3/T_3-ratio even more. The serum TSH and the TSH response to TRH was decreased, considered by the authors to be associated with the severe stress and consequently increased adrenal cortisol secretion, induced by cardiac surgery. As other possible related factors to the diminished secretory response of the anterior pituitary to TRH, they suggest the more rapid clearance of the administered TRH through the CPB heart-lung machine or the hypothermia per se [10].
In 1991 Holland et al. [12] also investigated (14) patients, aged between 18 and 67 years, undergoing CPB to determine the effect on concentrations of thyroid hormones. They found the concentrations of total T_3 progressively decreasing from preoperative baseline on and remaining depressed throughout CPB up to at least 24 hours after CPB (last measurement). The concentrations of rT_3 somewhat decreased during CPB and only increased significantly postoperatively, demonstrating a fourfold increase at 24 hours postoperatively.
In contrast to the findings of Robuschi et al. [11], there was no change in TSH concentration [12]. The postoperative changes were not due to hemodilution, since the albumin returned to normal by 2 hours after CPB. The authors also conclude that the changes in total T_3 and rT_3 most likely were secondary to alteration in thyroid hormone metabolism and not, for example, to uptake and degradation by the extracorporeal circuit, because otherwise all the, structurally similar, thyroid hormones would have been affected equally [12].

CONCLUSION

In conclusion, as a consequence of cardiac surgery with CPB and hypothermia, concentrations of thyroid hormones are changed. T_3 shows a striking de-

crease beginning with the induction of anaesthesia, decreases further during CPB and is being normalized 1 week after surgery. The rT_3 firstly decreases during anaesthesia and CPB, only to start increasing shortly after surgery. One week after surgery the rT_3 has returned to normal values.
In non-surgical patients with NTI, the extent of alteration in thyroid hormone concentrations is related to the severity of the underlying disorder, in terms of mortality and days of admission, being a measure for the health status [7]. Thus, the rT_3/T_3-ratio may be both characteristic and prognostic in the outcome of patients undergoing cardiac surgery with CPB and hypothermia.
In contrast to the supposed protective and adaptive role of the altered thyroid hormone metabolism in patients with NTI, it has recently been suggested that the low T_3 plasma levels induced by CPB are detrimental [13]. According to clinical and laboratory data administration of T_3 might be useful for patients with a low T_3 syndrome after CPB to treat or prevent low cardiac output due to depressed ventricular function, paralleling the decrease in total T_3 [12,13]. However, this 'treatment' remains controversial and as Clark [13] states "only blinded, randomized trials will provide the information necessary to substantiate the early investigational data supporting routine use of T_3 in cardiac operations".
Furthermore, one must keep in mind that several other, non-CPB related factors possibly influence the degree of thyroid hormone alterations. Many pharmacological agents, interfering with thyroid function tests are being used in the medical management of patients undergoing cardiac surgery; elderly with a cardiac disease often have concomitant disorders; and the (preoperative) nutritional state (especially a lack of carbohydrates) may also affect thyroid hormone metabolism.

REFERENCES

1. Felicetta JV. Effects of illness on thyroid function tests. Postgraduate Medicine 1989; 85: 213-220.
2. Hennemann G, Krenning EP. Pitfalls in the interpretation of thyroid function tests in old age and non-thyroidal illness. Hormone Res 1987; 26: 100-104.
3. Ingbar SH. The Thyroid Gland. In: Wilson JD, Foster DW (Eds.). Williams' Textbook of Endocrinology 1987; 17th. ed.: 682-742.
4. Docter R, Krenning EP, Jong M de, Hennemann G. The sick euthyroid syndrome: Changes in thyroid hormone serum parameters and hormone metabolism. Clinical Endocrinology 1993; 39: 499-518.
5. Visser TJ, Docter R. Production and metabolism of thyroid hormone (In Dutch). In: Wiersinga WM, Krenning EP (Eds.). Thyroid diseases. Alphen aan de Rijn, Samson Stafleu, 1988: 15-30.
6. Jong M de , Docter R, Hoek HJ van der, Vos RA, Krenning EP, Hennemann G. Transport of 3,5,3'-triiodothyronine into the perfused rat liver and subsequent metabolism are inhibited by fasting. Endocrinology 1992; 131: 463-470.
7. Krenning EP, Docter R, Visser TJ, Vos RA, Toor H van, Hennemann G. Sensitive serum TSH assay. The initial diagnostic tool in evaluation of thyroid function. JDR Journal for Drugtherapy and Research 1987; 12: 271-277.
8. Lim C-H, Docter R, Krenning EP, Toor H van, Bernard B, Jong M de, Hennemann G. Transport of thyroxine into cultured hepatocytes: Effects of mild non-thyroidal illness and calorie restriction in obese subjects. Clinical Endocrinology 1994; 40: 79-85.
9. Zaloga GP, Chernow B, Smallridge RC et al. A longitudinal evaluation of thyroid function

in critically ill surgical patients. Ann Surg 1985; 201: 456-464.
10. Zhou Xiao P, Zhao Meng Y, Ji Yi Z, Guo Zong N, Kong Ling S. Dynamic observation on thyroid function in severe head injury. Chinese med J 1990; 103: 335-338.
11. Robuschi G, Medici D, Fesani F et al. Cardiopulmonary bypass: A low T_4 and T_3 syndrome with blunted thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH). Hormone Res 1986; 23: 151-158.
12. Holland FW, Brown PS, Weintraub BD, Clark RE. Cardiopulmonary bypass and thyroid function: A "Euthyroid Sick Syndrome". Ann Thorac Surg 1991; 52: 46-50.
13. Clark RE. Cardiopulmonary bypass and Thyroid hormone metabolism. In: The acute cardiovascular actions of thyroid hormone. Clark RE (Ed.). Ann Thorac Surg 1993; 56 (supplement): 35-42.

Chapter 3.3

DELIRIUM AFTER CARDIAC SURGERY: POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS

INTRODUCTION

In chapter 5.1 the potential role of various aminoacids, hormones and neurotransmitters in the occurrence of (the different aspects, clinical presentations and specific disease-related forms of) delirium were described. In this chapter the possible pathophysiological mechanisms in the appearance of delirium after cardiac surgery with cardiopulmonary bypass will be summarized.

CARDIAC SURGERY AND BRAIN DAMAGE

Cardiac surgery, probably more than any other major surgical procedure, is a serious insult to the integrative capacity of the body and especially the brain, due to the unusual physiology imposed by CPB [1]. Advances in anaesthetic and surgical techniques and in equipment have all contributed to the reduction in morbidity and mortality from cardiac surgery with CPB [2]. Nonetheless, there is still considerable neurological morbidity associated with this type of surgery, most probably due to cerebral (gas, air, fat and platelet) microemboli and hypoperfusion [1,2]. Microemboli have been shown in the arterial circulation during extracorporeal perfusion with doppler ultrasound and in retinal circulation with fluorescein angiography [2]. The pressure required for optimum cerebral perfusion is not known. Hypoperfusion probably only plays a considerable role in causing postoperative neurological deficits in brain-damaged patients with impaired cerebral autoregulation leading to pressure dependent cerebral blood flow [3]. The importance of the short-lived neurological impairments like primitive reflexes and impaired coordination is unclear and the long-lived neurological deficits such as diminished neuropsychological performance are difficult to interpret and possibly not unique to patients undergoing cardiac surgery with CPB [2,4]. The only variable found to correlate significantly with neuropsychological outcome was the fall in haemoglobin concentration with haemodilution during extracorporeal circulation [2,4]. Thus, neurological damage sometimes occurs, the risk of permanent damage probably being only 0.2% [2]. There is a risk of subtle intellectual impairment, possibly more likely with increasing age and duration of CPB (especially beyond two hours), but to date there are apparently no known strong predictors [2-4].

Computed Tomography (CT) of the brain only shows abnormalities in patients who have suffered major neurological events [5]. Magnetic resonance imaging (MRI) in six patients undergoing coronary bypass surgery, showed brain swelling with reduction in size in all six patients on the immediate postoperative scan without clinically major neurological deficit or pronounced confusion. The later MRI's (after 6-18 days) did no longer exhibit these abnormalities. The authors argue that the brain swelling could be due to cytotoxic oedema induced by microemboli, hypoperfusion or haemodilution after CPB. Further study on the association of the cerebral swelling with major non-cardiac surgery (without CPB), and on the relation to postoperative morbidity is necessary [5].

CARDIAC SURGERY, DELIRIUM AND NEUROTRANSMISSION

Cardiac surgery with CPB is a physiologically stressful event leading to elevated plasma levels of glucocorticoids and dopamine and the so-called low T_3 syndrome. Glucocorticoids induce the enzyme tryptophan pyrrolase in the liver, causing a reduction of the plasma concentration of tryptophan. The synthesis of serotonin in the brain depends on the availability of its precursor tryptophan. Thus, a reduced plasma availability of tryptophan may lead directly to decreased activity of cerebral serotonin. Moreover, a stressful, catabolic state may reduce tryptophan transport across the blood-brain barrier because the plasma concentration of the aminoacids valine, isoleucine, leucine, tyrosine and phenylalanine, which compete with tryptophan for the transport-carrier at the blood-brain barrier, is increased due to degradation of muscle proteins. Therefore, delirium after cardiac surgery may be related, among others, to decreased cerebral tryptophan and serotonin deficiency [5,6].

Furthermore, an excess of both glucocorticoids and dopamine causes a decrease of TSH by inhibiting the release of TRH, in this way possibly preventing stimulation of the thyroid and maintaining the adaptive low T_3 syndrome. A low T_3 level may cause 1. a diminished transport of aminoacids and carbohydrates, possibly giving rise to substrate deficiency, thus inhibiting the synthesis of the directly substrate dependent neurotransmitters, especially acetylcholine and serotonin, and 2. a generally decreased metabolism through reduced synthesis of ATP.

The synthesis of various neurotransmitters is altered both in cerebral hypoxic hypoxia, anaemic hypoxia and thiamine deficiency, conditions often occurring around surgery and CPB. The consequently extracellular excess of dopamine and glutamate in the brain have been implicated in cellular damage and some features of delirium. The decline in cerebral cholinergic activity, occurring in association with hypoxia and substrate and thiamine deficiency, may also play an important role in the occurrence of delirium after CPB, next to possible blockade of cholinergic transmission by the use of different anticholinergic medications. Hypoxia does not seem to influence the synthesis of serotonin and noradrenaline directly.

In conclusion, delirium after cardiac surgery with CPB may be the result of a state of catabolism, causing an imbalance of cerebral neurotransmission with a relative hyperactivity of the dopaminergic (noradrenergic and glutamate?) system and hypoactivity of the cholinergic and serotonergic system. Direct action on the neuronal cell and alterations in neurotransmitter release furthermore influence intracellular second messenger systems, which again may change neurotransmitter synthesis.

REFERENCES

1. Clark RE. Cardiopulmonary bypass and thyroid hormone metabolism. In: Clark RE (Ed.). The acute cardiovascular actions of thyroid hormone. Ann Thorac Surg 1993; 56 (supplement): 35-42.
2. Editorial. Brain damage and open-heart surgery. The Lancet 1989; 338: 364-366.
3. Gilston A. Brain damage after cardiac surgery (Letter to the Editor). The Lancet 1986; 335: 1323.
4. Shaw PJ, Bates D, Cartlidge NEF, Heaviside D, Julian DG, French JM, Heaviside D, Julian DG, Shaw DA. An analysis of factors predisposing to neurological injury in patients undergoing coronary artery bypass operations. Quart J Med 1989; 72: 633-646.
5. Harris DNF, Baily SM, Smith PLC, Taylor KM, Oatridge A, Bydder GM. Brain swelling in the first hour after coronary artery bypass surgery. The Lancet 1993; 342: 586-587.
6. Mast RC van der, Fekkes D, Moleman P, Pepplinkhuizen L. Is postoperative delirium related to reduced plasma tryptophan? The Lancet 1991; 338: 851-852.
7. Caston JC, Utley JR, Fleming HE. Endocrine marker for l-tryptophan response in cardiopulmonary bypass delirium patients: Case reports. Advances in Therapy 1989; 6: 161-179.

Chapter 3.4

IS POSTOPERATIVE DELIRIUM RELATED TO REDUCED PLASMA TRYPTOPHAN: A PRELIMINARY STUDY

R.C. van der Mast, D. Fekkes, P. Moleman, L. Pepplinkhuizen

Adapted from:
The Lancet 1991; 338: 851-52

INTRODUCTION

Delirium is transient organic mental syndrome of acute onset characterized by global impairment of cognitive functions, reduced consciousness, attentional abnormalities, increased or decreased psychomotor activity, and a disordered sleep-wake cycle [1]. It is a complication of a variety of medical conditions, especially open-heart surgery, and may confer increased morbidity, institutionalization, prolonged hospital stay, and increased risk of mortality [2,3,4]. Although according to Smith and Dimsdale the incidence of postcardiotomy delirium has remained fairly constant at about 30% for the past 25 years, it was shown in chapter 1.3 that their conclusion, based on meta-analysis, is questionable. The reported rates of postoperative delirium after cardiac surgery are in general high, but the current incidence is unknown as is its cause [5]. Major surgery, especially after prolonged disease, is stressful and induces a catabolic state, as indicated by, for example, elevated serum cortisol [1]. We hypothesised, according to Skaug, that the delirium in the patient, described hereafter, was caused by cerebral tryptophan deficiency due to a the catabolic state [6].

CASE

A 14-year-old girl had undergone cardiac transplantation for end-stage heart failure after a prolonged hospital stay. The postoperative course was complicated by sepsis and skin necrosis, and she also developed severe psychiatric symptoms. Delirium of unknown etiology was diagnosed. Laboratory investigations and a computed tomography scan of the brain were normal; there was no hypoxia and the only drug that could be related to the occurrence of delirium was prednisone (20 mg per day). We wondered whether delirium was caused by a tryptophan deficiency resulting from a severe catabolic state and prednisone medication. The patient's plasma tryptophan concentration was 16 micromol/l, which is well below normal values. She was treated by oral administration of 6 gram of L-tryptophan (2 gram before every meal) and within 3 days the psychiatric symptoms disappeared completely.

METHOD

To test the hypothesis that postoperative delirium may be related to reduced plasma tryptophan due to a catabolic state, blood samples were drawn from 7 delirious patients (6 men, 1 woman) within 5 days of cardiac surgery. Plasma concentrations of tryptophan were determined by high-performance liquid chromatography and other aminoacids were measured with an aminoacid analyzer [7]. The plasma tryptophan ratio was calculated by dividing the plasma tryptophan concentration by the sum of the concentrations of the other large neutral aminoacids-ie, valine, isoleucine, leucine, tyrosine, and phenylalanine [8]. Results were expressed as mean (SD) and compared with the values of a group of 8 non-delirious patients (7 men, 1 woman) who had the same type of surgery. A second group of controls were 21 healthy individuals (11 men, 10 women) from among the hospital staff.

Differences in plasma tryptophan concentrations and plasma tryptophan ra-

Table

Biochemical and surgical data of patients and controls

	Age (yr)	Plasma Tryptophan (μmol/l)	Plasma tryptophan ratio	Type of sugery
Patients (sex)				
1 (M)	62	30	4.9	CABG
2 (F)	66	31	4.5	AAR
3(M)	65	37	5.3	CABG
4(M)	73	25	3.6	CABG
5(M)	70	21	3.2	CABG
6(M)	57	23	3.6	VSR
7(M)	76	43	5.6	VR
Mean(SD) values	67(7)	30(8)*	4.4(0.9)#	
Postoperative controls (n=8)				
Mean(SD) values	65(9)	52(11)	6.6(1.4)	CABG (n=5) CABG+VR (n=2) VR (n=1)
Healthy controls (n=21)				
Mean(SD) values	34(4)	48(9)	7.7(1.5)	

CABG=coronary artery bypass grafting; AAR=ascending aorta replacement for aortic aneurysm; VSR=ventrical septal repair; VR=valve replacement.
**p=0.0001, #p<0.0001, patients vs both control groups*

tios were tested with one-way analysis of variance, followed by the Student-Newman-Keuls multiple comparison procedure (at the 0.05 level of significance). Homogeneity of variances was verified with Cochran's C-test.

RESULTS

The mean plasma tryptophan concentration of the 7 delirious patients was significantly lower than the mean plasma tryptophan concentrations of postoperative and healthy controls (table). The same was also true of the plasma tryptophan ratio. No significant differences were found between the control groups. Postoperative electrolyte disturbances were equally present in both groups of patients.

DISCUSSION

Tryptophan is the precursor of (cerebral) serotonin, a neurotransmitter involved in functions such as aggressive and impulsive behaviour, mood, motor activity and sleep that are disturbed during delirium. The amount of func-

tional serotonin in the central nervous system is dependent on -among other factors- the transport of its precursor tryptophan across the blood-brain barrier. A catabolic state may reduce tryptophan transport because of two important mechanisms: 1) the plasma concentration of the aminoacids valine, isoleucine, leucine, tyrosine and phenylalanine, which compete with tryptophan for the transport-carrier at the blood-brain barrier, is increased due to degradation of muscle proteins; and 2) the plasma concentration of tryptophan is reduced because of induction of tryptophan pyrrolase [8,9].
Our results suggest a role for reduced tryptophan availability from plasma in postcardiotomy delirium, but replication of these findings in larger groups of patients and in a prospective research design is necessary.

REFERENCES

1. Lipowski ZJ. Delirium: Acute Confusional States. New York: Oxford University Press, 1990.
2. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990; 263: 1097-1101.
3. Rogers MP, Liang MH, Daltroy LH. Delirium after elective orthopedic surgery: risk factors and natural history. Int J Psychiatry Med 1989; 19: 109-121.
4. Hemert AM van, Mast RC van der, Hengeveld MW, Vorstenbosch M. Excess mortality in general hospital patients with delirium. A 5-year follow-up of 519 patients seen in psychiatric consultation. J Psychosomatic Res 1994; 38: 153-154.
5. Smith LW, Dimsdale JE. Postcardiotomy delirium: Conclusions after 25 years? Am J Psychiatry 1989; 146: 452-458.
6. Skaug OE. Mental disturbances after major surgery: A stress reaction due to tryptophan deficiency in the brain. Report of a case successfully treated with tryptophan. Tidsskr Nor Laegeforen 1989; 104: 97-111.
7. Bruinvels J, Pepplinkhuizen L. Impaired glycine-serine conversion and increased plasma taurine levels in episodic psychotic patients with psychedelic symptoms. J Psychiatry Res 1984; 18: 307-318.
8. Fernström JD, Wurtman RJ. Brain serotonin content: Physiological regulation by plasma neutral amino acids. Science 1972; 178: 414-416.
9. Lehman J. Tryptophan deficiency stupor: A new psychiatric syndrome. Acta Psychiatr Scand 1982; suppl 300: 1-46.

Chapter 4

AIMS AND METHODS

INTRODUCTION

As was mentioned before, the incidence of postcardiotomy delirium varies from 2 to 57%, depending on the research design, the study sample, the assessment methods and the definition of delirium. Generally, cardiac surgery has been associated with a rather high rate of postoperative delirium [1]. However, there are few data about the current incidence and nothing is known about the precise pathophysiological processes by which (postcardiotomy) delirium is mediated. Several risk factors have been studied, but no one has been consistently designated, due to a lack of adequate replication studies [1]. Postoperative delirium is considered to have multiple possible causes and to represent the result of a combination of preoperative, intraoperative and postoperative factors.

The hypothesis that delirium after cardiac surgery with cardiopulmonary bypass (CPB) may be related to reduced plasma tryptophan, due to a catabolic state, and altered cerebral serotonin metabolism was indeed suggested from the findings of our aforementioned study and from a few case reports, but replication in larger groups of patients, in a prospective design, is necessary [2,3]. Moreover, several other neurotransmitter alterations and deficiencies have been hold responsible for the occurrence of (postcardiotomy) delirium, notably acetylcholine and noradrenaline [3,4,5].

AIMS

Patients undergoing various types of elective cardiac surgery were prospectively studied to investigate:

1. The current incidence of delirium after (various types of) cardiac surgery.
2. The risk factors associated with postcardiotomy delirium.
3. The pathophysiology of delirium after cardiac surgery-i.e.:
   a. the role of reduced cerebral tryptophan availability
   b. the role of changes in plasma concentrations of the other large neutral aminoacids
   c. the influence of physiological stress c.q. a catabolic state in relation to plasma concentrations of the aminoacids and the occurrence of delirium after cardiac surgery
4. The clinical course and outcome.

PATIENTS AND METHODS

PATIENTS

The study was conducted in the Thoraxcentre of the University Hospital Dijkzigt, which is a large (approximately 1000 beds), inner-city teaching hospital in Rotterdam, the Netherlands. The study took place from may 1991 to november 1992. During this period 330 patients consented to join the study; only fifteen patients (5%) refused to participate. All patients speaking Dutch and being older than 21 years of age, admitted for elective cardiac surgery (coronary artery bypass graft (CABG), valve replacement (VR), CABG+VR, and surgery for heart defects with or without CABG and/or VR), were eligible for the study. From may 1991 - april 1992, 110 consecutive patients, awaiting

elective cardiac surgery, were recruited from only one of the cardiologic wards and one of the preoperative, outpatient clinics because of insufficient availability of study personnel. From april 1992 - november 1992 all (n=221) patients, consecutively admitted to the cardiologic wards and outpatient clinics were included. Patients were excluded if unable to complete the questionnaires, mostly due to language problems. During the study 34 (10%) of the 330 originally included patients dropped out: 6 patients died during or shortly after surgery, 7 patients were operated on elsewhere, 4 patients still refused, in 8 cases there were problems with the blood sampling and another 9 patients were lost for various reasons. The final study sample consisted of 296 patients.

PREOPERATIVE ASSESSMENT

After informed consent was obtained patients were assessed according to a standardized psychiatric and psychometric evaluation, depending on the waiting list, usually one to four weeks before surgery. The psychiatric and psychometric evaluation included somatic and psychiatric history, demographic and medication data and the following (self-rating) scales: the Mini Mental State Examination as a cognitive screenings test [6], the 30-item version (being the least dependent on somatic items) of the General Health Questionnaire to screen for possible psychiatric disturbances [7-10], the Münchner Alcohol Test to detect possible alcohol abuse [11,12] and the Daily Activity List [13,14]. Besides, on the day before surgery, patients were asked to fill in the Profile of Mood States [15].

Just before induction of anaesthesia (between 8 and 11 a.m.) blood samples were drawn for the following laboratory investigations:

1. levels of cortisol as a measure for physiological stress
2. levels of albumin, prealbumin, T_3 and reverse T_3 as measures for catabolic state. The ratio rT_3:T_3 was calculated as a measure for catabolism
3. levels of total plasma tryptophan, the other large neutral aminoacids-ie, valine, leucine, isoleucine, tyrosine and phenylalanin; and methionine, serine and taurine [2]. The plasma ratios of tryptophan, tyrosine and phenylalanine were calculated by dividing the plasma concentration of the concerning aminoacid by the sum of the other five large neutral aminoacids [2]. The molar ratio tryptophan:albumin was used as a measure for the amount of free tryptophan. The ratio TAU:METxSER was determined as a measure for the amount of methyl donors
4. folic acid and vitamins B1, B6 and B12, because of their major importance in the metabolism of both tryptophan and most of the other large neutral aminoacids.

POSTOPERATIVE ASSESSMENT

On the first postoperative day 8 a.m. (fasting) blood samples were drawn for plasma levels of cortisol, albumin, prealbumin, the ratio reverse T_3:T_3, tryptophan, and the other aminoacids.

Type of surgery, duration of surgery, time on cardiopulmonary bypass, dura-

tion of hypothermia, lowest nasal temperature, minutes of mean systolic blood pressure ≤ 60 mm Hg. (generally considered the value below which cerebral hypoxia occurs) and (amount of) medications were recorded.
On day 2 through 5 or earlier, if requested because of behavioural problems, mental status examination and chart review were performed by a psychiatrist for the presence of delirium according to DSM-III-R criteria [16]. Information of the medical staff and relatives of the patients for signs of delirium was included. For a diagnosis of delirium symptoms had to be present for at least 24 hours and not only on the first postoperative day, which was excluded because of the difficulty of distinguishing between true delirium and possible residual effects of anaesthesia. Besides, a delirium occurring later than day 5 postoperatively was not considered a postcardiotomy delirium, not being directly related to the cardiac surgery. Patients were rated on the Symptom Rating Scale for Delirium (DRS) [17], the cognitive status being assessed with the Mini Mental State Examination [6]. In case of delirium, patients were followed up and rated as long as the delirious symptoms continued. When communication was impossible as a consequence of (prolonged) intubation and/or sedation, patients were considered 'probable delirious' (though formally not assessable) in case they needed haloperidol for treating supposed delirious symptoms like inadequate behaviour, probable signs of hallucinations and/or suspicion, agitation or apathy, inversed day-night rythm and severe cognitive deficits e.g. inability to cooperate with formal mental status testing. Thus, next to a diagnosis of delirium according to DSM-III-R criteria and the score on the DRS, haloperidol medication was regarded as one of the outcome measures.
All patients were followed up during hospitalization to compare for postoperative complications, medications, length of hospital stay, mortality and living situation after discharge between delirious and non-delirious patients. Six months after discharge all patients were interviewed by telephone to gather information about survival, living situation and physical impairment.

MANAGEMENT OF ANAESTHESIA AND CARDIOPULMONARY BYPASS

ANAESTHESIA

The anaesthetic management included premedication with a benzodiazepine: lorazepam (Temesta®) or flurazepam (Dalmadorm®); and induction and maintenance with pavulon, moderate to high doses of fentanyl, and midazolam (Dormicum®) or propofol (Diprivan®). Ventilation consisted of oxygen in air (f_iO_2 40-60 %). Hemodynamic changes were treated with vasopressors (efedrine or noradrenaline) and vasodilators (nitroglycerine, ketanserine, fentolamine or nitroprusside). As inotropics were used dopamine or dobutamine and as diuretics furosemide or sometimes bumetanide. Other occasionally administered intraoperative medications were corticosteroids, lidocaine and chlorpromazine. All patients received Albumin (200g/l), pasteurized plasma-unit so-

lution (=albumin 40g/l) or Haemaccel (35g/l polygeline) as blood substitute transfusions. Postoperatively, in addition to intravenous fluids, diuretics (furosemide=Lasix®), H_2-receptor blockers (ranitidine=Zantac®) and antibiotics patients received morphine sulphate or pethidine for analgesia and non-standardized supplemental doses of midazolam or propofol for sedation, if necessary. A few patients received corticosteroids. Haloperidol (Haldol®) was administered for symptoms of delirium. Consequently, haloperidol administration is included in the analysis of onset, severity and course of delirium. In a few patients delirious agitation could not be adequately managed with haloperidol, in which cases propofol was used for a longer than the immediate postoperative period.

CARDIOPULMONARY BYPASS

Patients were given 300 IU/kg of intestinal mucosa heparin, supplemented as needed to maintain an activated clotting time of about 600 seconds. Membrane oxygenators were used. The circuit was primed with Haemaccel ±1700 ml, Mannitol 40 g, Albumin 20 g, Bicarbonate 50 meq and 8500 IU Heparin. Blood was added as necessary to achieve a hematocrit value of 20 mmol/l during bypass. An arterial line filter (screen 40 micron) was used. Nonpulsatile perfusion with either a rollerpump or a centrifugalpump was given at an index of 2.4 l/min/m^2 at normothermia and 1.8 l/min/m^2 at hypothermia (nasal temperature 28°C). Arterial pO_2 was kept at 20 kPa (actual temperature) and acid-base management was done with Alpha-stat.

DESCRIPTION OF THE RESEARCH INSTRUMENTS

MINI MENTAL STATE EXAMINATION (MMSE) [6,18,19]

The MMSE is a widely used, brief and standardized method for assessing current cognitive mental status both in clinical practice and in research, that screens for intellectual impairment and allows comparison of performance across time and among patients. It consists of 11 items assessing orientation, attention, immediate and short-term recall, language skills, the ability to follow simple verbal and written commands and one construction question. The maximum total score is 30. A total score of less than 24 indicates diffuse cognitive dysfunction. Using a cut-off score between 23 and 24 (23/24), the sensitivity and specificity of the MMSE has been reported to be 87% and 82% respectively. Age and education have a demonstrable influence on the score. It has to be remembered that the MMSE is a screening test and does not identify specific disorders such as dementia or delirium.

30-ITEM VERSION OF THE GENERAL HEALTH QUESTIONNAIRE (GHQ) [7-10]

The GHQ is a self-report screening questionnaire for the detection of non-psychotic psychiatric illness in medical practice and is also used as a descriptive measure of psychiatric symptoms [7,8]. The GHQ-items are rated on a 0-0-1-1

scale and added up to a total score. We used the separate 30-item version of the GHQ, which has been derived from the original 60-item questionnaire by excluding symptoms that are commonly present in medically ill patients [8]. The GHQ has been translated into Dutch by Koeter & Ormel [9] and has been validated as a case-finding instrument in patients of a Dutch general medical outpatient clinic by van Hemert et al. [10]. The GHQ is based on recent change in an individual's psychological state and does not identify all patients with chronic mental disorders. Specificity and sensitivity depend on the nature of the target population and optimal discrimination depends on the correct choice of threshold [8,9]. For example, it is possible to improve specificity in a medically ill population by raising the cut-off threshold, of course consequently reducing sensitivity. For the separate version of the GHQ-30 van Hemert et al. found a sensitivity of 0.73 and a specificity of 0.74 at a cut-off level of 10/11 compared with, for example a sensitivity of 0.85 and a specificity of 0.70 at a cut-off level of 8/9, tested against the Present State Examination-Index of Definition 5+ case criterion [10]. Next to the mean scores, the delirious patients were compared with the non-delirious patients, using different cut-points to find the optimal cut-off for discrimination of delirious and non-delirious patients. Since factor analysis of the GHQ-30 yielded different subscales corresponding to the factors anxiety, feelings of incompetence, depression, difficulty coping and social isolation, a possible association between these separate factors and delirium was examined [8].

MÜNCHNER ALCOHOL TEST (MALT) [11,12]
The MALT is a screening instrument for alcoholism especially suitable in medical populations. The Dutch version has been validated by van Limbeek & Walburg [10]. The MALT consists of two complementary sections: a 24-item self-assessment (MALT-S) and a 7-item physician's assessment (MALT-F). The maximum score on the MALT-S is 24 points, on the MALT-F 28 points. Because in one research study concerning alcohol abuse among general hospital in-patients the MALT-S appeared to be more sensitive than the MALT, the MALT-S was used to screen for alcohol abuse [20]. A score of ≥ 7 is suggestive for alcohol dependence and 4-6 for alcohol abuse.

DAILY ACTIVITY LIST (DAL) [13,14]
Limitations in daily activities were measured with the Daily Activity List, a self-rating questionnaire consisting of 11 items concerning self-care activities, mobility, and physical, role and leisure activities. The DAL gives an impression of the influence of a somatic illness (i.c. cardiac disease) on the capacity to perform a variety of activities that are normal for people in good physical health (= functional status) and is used as a measure of physical health. The DAL consists of 11 items, which are rated on a 0/1 scale and add up to a total score of 11 points.

PROFILE OF MOOD STATES (POMS) [15]

The POMS is a self-rating scale for varying moods. The original POMS consisted of 65 items, divided among 7 mood categories. The Dutch, shortened 32-item version of the POMS was used, measuring 5 dimensions: depression (8 items), anger (7 items), fatigue (6 items), vigour (5 items) and tension (6 items). The score of the different items adds up from 0 to 4 points, the total score amounting 128.

THE SYMPTOM RATING SCALE FOR DELIRIUM (DRS) [17]

The DRS is a 10-item, symptom rating scale for delirium which addresses 10 areas characteristically affected in delirium. It is rated by the clinician using all available information from the patient interview, mental status examination, medical history and tests, nursing observations, family reports etc. The DRS rating is based on at least a 24-hour period. Each item is scored by choosing one best rating. The total DRS score equals the sum of the 10 item scores. The maximum possible score is 32. The DRS appears to identify delirium and quantitate its severity. The interrater reliability, as described by Trzepacz et al., is high with an intraclass correlation of 0.97.

STATISTICAL ANALYSIS

The data were analyzed using the statistical package SPSS/PC+ version 4.0.1. Methods of statistical analysis will be explained in the corresponding chapters.

REFERENCES

1. Smith LW, Dimsdale JE. Postcardiotomy Delirium: Conclusions after 25 Years? Am J Psychiatry 1989; 146: 452-458.
2. Mast RC van der, Fekkes D, Moleman P, Pepplinkhuizen L. Is postoperative delirium related to reduced plasma tryptophan? The Lancet 1991; 338: 851-852.
3. Caston JC, Utley JR, Fleming HE. Endocrine marker for l-tryptophan response in cardiopulmonary bypass delirium patients: Case reports. Advances in Therapy 1989; 6: 161-179.
4. Lindesay J, Macdonald A, Starke I. The neuronal basis of delirium. In: Delirium in the elderly. Oxford University Press: Oxford, 1990; chapter 4: 68-75.
5. Ross CA. CNS arousal systems: possible role in delirium. In: Miller NE, Lipowski ZJ (eds). Delirium. Advances in research and clinical practice. International Psychogeriatrics 1991; 3: 353-373.
6. Folstein MF, Folstein SE, McHugh PR. 'Mini Mental State': a practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975; 12: 189-198.
7. Goldberg DP. The detection of psychiatric illness by questionnaire. Maudsly monograph number 21. Oxford University Press: London, 1972.
8. Huppert AH, Eurof Walters D, Day NE, Elliott BJ. The factor structure of the General Health Questionnaire (GHQ-30). A reliability study on 6317 community residents. Brit J Psychiatry 1989; 155 : 178-185.
9. Koeter MWJ, Ormel J. General Health Questionnaire. Nederlandse bewerking (Dutch version). Swets and Zeitlinger B.V.: Lisse, 1991.
10. Hemert AM van, Heijer M den, Vorstenbosch M, Bolk JH. Detecting psychiatric disorders in medical practice using the General Health Questionnaire. Why do cutoff levels vary ? Accepted for publication.
11. Limbeek J van, Walburg JA. De vroege signalering van alcoholproblematiek (The early detection of alcohol problems). Swets and Zeitlinger B.V.: Lisse, 1987.
12. Feuerlein W, Ringer C, Küfner H, Antons K. Diagnosis of alcoholism: The Münich

Alcoholism Test (MALT). Currents in Alcohol 1979; 7: 137-147.
13. Kaptein AA, Dekker FW, Dekhuijzen PNR, Wagenaar JPM, Janssen PJ. Patiënten met chronische luchtwegobstructie: scores op NPV en SCL-90 en hun relaties met functionele capaciteit en belemmeringen in dagelijkse activiteiten. Gezondheid en Samenleving 1986; 7: 10-19.
14. Stewart AL, Ware JE, Brook RH. Advances in the measurement of functional status: Construction of aggregate indexes. Medical Care 1981; 19: 473-488.
15. Wald FDM, Mellenbergh GJ. De verkorte versie van de Nederlandse vertaling van de Profile of Mood States (POMS). Ned Tijdschr Psychol 1990; 45: 86-90.
16. Diagnostic and Statistical Manual of Mental Disorders. ed 3 revised. Washington, DC, American Psychiatric Association, 1987.
17. Trzepacz PT, Baker RW, Greenhouse J. A Symptom Rating Scale for Delirium. J Psychiat Res 1988; 23: 89-97.
18. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-bases norms for the Mini-Mental State Examination by age and educational level. JAMA 1993; 269: 2386-2391.
19. Cummings JL. Editorial. Mini-Mental State Examination. Norms, Normals, and Numbers. JAMA 1993; 269: 2420-2421.
20. Smals GLM, Mast RC van der, Speckens AEM, Schudel WJ. Alcohol abuse among general hospital in-patients according to the Münich Alcoholism Test (MALT). Gen Hos Psychiatry 1994; 16: 125-130.

Chapter 5

DETECTING AND MEASURING THE SEVERITY OF DELIRIUM WITH THE SYMPTOM RATING SCALE FOR DELIRIUM

INTRODUCTION

The comparison of the findings of different research studies on delirium is being hampered by methodological problems. First, the criteria for defining delirium have changed over time and are still being refined and operationalized. Second, the groups chosen for investigation and the patient selection criteria differ. Third, several case finding methods have been used in the study of delirium to detect the syndrome such as mental status questionnaires, psychomotor tests, clinical interviews, symptom rating scales and EEG assessment [1-3].

In this study a diagnosis of delirium after cardiac surgery was based on mental status examination using the DSM-III-R criteria. Furthermore, the Symptom Rating Scale for Delirium (DRS) was administered for measurement of severity of symptomatology [4].

The DRS is a 10-item scale which addresses 10 areas characteristically affected in delirium, namely: 1) temporal onset of delirium, 2) perceptual disturbances, 3) hallucination type, 4) delusions, 5) psychomotor behaviour, 6) cognitive status during formal testing, 7) physical disorder, 8) sleep-wake cycle disturbance, 9) lability of mood and 10) variability of symptoms (see addendum) [4]. The items for the scale were chosen on the basis of descriptions of delirium in the literature and the DSM-III and are specifically described. The DRS is rated by the clinician using all available information from the patient interview, mental status examination, medical history and tests, nursing observations, family reports etc. The DRS rating is based on at least a 24-hour period. Each item is scored by choosing one best rating of the 3-5 possible ratings. The total DRS score equals the sum of the 10 item scores. The maximum possible score is 32.

Trzepacz et al. [4] found that the DRS identified delirium and quantified its severity. The DRS successfully distinguished delirious patients (n=20) from control patients with dementia (n=9) and schizophrenia (n=9) and from medically ill inpatients without a psychiatric disorder (n=9), referred for psychiatric consultation. No overlap existed in the distribution of scores between the delirious group and any of the control groups. The interrater reliability, as described by Trzepacz et al. [4], was high with an intraclass correlation of 0.97.

No other validity study has been published. A major drawback of the DRS is that its scoring relies on clinical judgements based on unstructured clinical assessment, making it expensive to administer (e.g. by a psychiatrist) and difficult to standardize [1]. Also, the DRS makes no distinction between different clinical types of delirium. According to Trzepacz, analysis of the original data [4] for only delirious patients suggested a two-factor structure of the DRS (personal communication).

In this study, the assumption is tested that the DRS is one hierarchical scale, meaning that each of the ten area scored in the DRS is specific for the severity of delirium under evaluation. The hierarchical structure is demonstrated, for example, by the items 3 and 4 (see addendum). On the one hand, if one of these items is rated positively, it is to be expected that in almost all cases also item 2 will be scored positively. On the other hand, a positive scoring of item

2 does not necessarily mean that the item 3 and/or 4 will be rated positively. In our opinion, this reflects a difference in severity of delirium, in the first case the patient being more severely delirious than in the second case.

METHODS

Postoperatively, on day 3 and 4 (and day 5 for the first hundred study patients) or earlier, if requested because of behavioural problems, mental status examination and chart review was performed for the presence of delirium according to DSM-III-R criteria (see chapter 2). All available information from the medical staff and relatives of the patients for signs of delirium was included. For a diagnosis of delirium symptoms had to be present for at least 24 hours and not only on the first postoperative day, which was excluded because of the difficulty of distinguishing between onset symptoms of delirium and possible residual effects of anaesthesia. A delirium occurring later than day 5 postoperatively was considered not to be directly related to the cardiac surgery and therefore not included. At the same time, all patients were rated on the DRS, yielding at least two DRS scores for each patient. The cognitive status including general cognitive functions, orientation, attention and concentration was assessed using the Mini Mental State Examination. In case of delirium patients were followed up every day for mental status examination and scoring of the DRS. All patients were rated by one of the two researcher-psychiatrists.

STATISTICAL ANALYSIS

The DRS scores on day 3 postoperatively (DRS 3) and, since not all patients became delirious on the same day, the maximum DRS (DRS max.) scores of delirious and non-delirious patients were compared applying statistics for ordinal variables. Boxplots, showing the median and the location of the first and third quartile, for the DRS 3 and DRS max. scores are presented for both delirious and non-delirious patients. The frequencies of each of the item scores of the DRS 3 and DRS max. are shown. Spearman rankorder correlations were performed to analyze the relationship between the item scores and the corrected item total-score (item total-score minus value of item it is correlated with). To examine the presence of underlying dimensions factor analysis, followed by varimax rotation, was performed on the resulting correlation matrix. Subgroups of delirious patients were sought by means of cluster analysis.
To test the scalability of the DRS, making the assumption of a hierarchical structure of the scale, Mokken Scale Analysis, a stepwise search procedure, was done and the reliability coefficient was computed, after dichotomizing the items of the DRS [5-7].

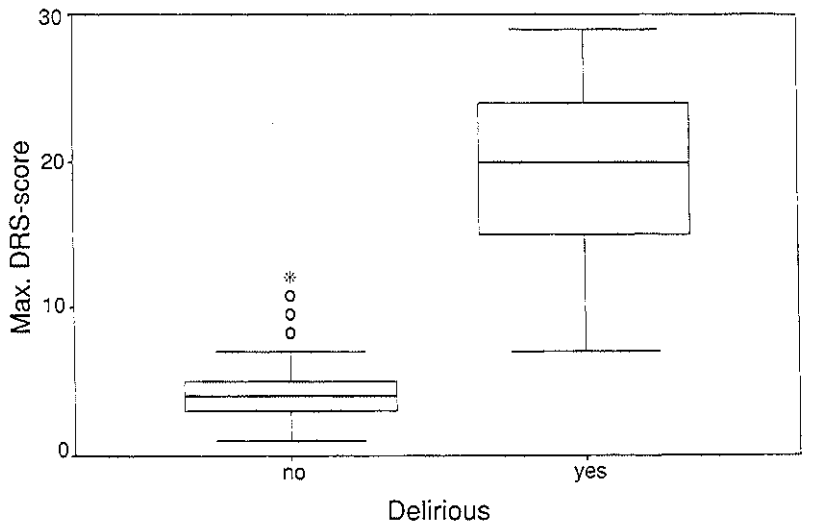
RESULTS

The DRS 3 scores ranged from 2-29 for the delirious group compared to a range from 1-9 for the non-delirious group. The DRS max. scores ranged from 7-29 in the patients with delirium and from 1-11 in the non-delirious patients. In figure 1 and 2 the boxplots of the DRS 3 and DRS max. scores for both

groups are presented. The median DRS 3 score was 14 for the delirious patients and 4 for the non-delirious patients, while the median DRS max. score for both groups was 20 and 4, respectively. The small overlap in the DRS max. scores indicated that the DRS has high discriminant validity.

Figure 1
Boxplots of Delirium Rating Scale scores on day 3, postoperatively, for delirious (n=254) and non-delirious patients (n=29)

Figure 2
Boxplots of maximum scores on the Delirium Rating Scale for delirious (n=36) and non-delirious patients (n=256)



However, contrary to the findings of Trzepacz et al. [4], the lowest DRS max. scores of the delirious patients were in the range of the higher scores of the non-delirious patients due to the fact that, in some cases, at the time of the first possible rating -after having been intubated and/or sedated- patients were no longer (fully) delirious.

In table 1 and table 2 the frequencies of the DRS 3 and DRS max. item-scores, respectively, are shown for delirious and non-delirious patients.

Table 1

The frequency of the DRS-item scores on day 3, postoperatively, for delirious (n=40) and non-delirious patients (n=256)

DRS-items	Ratings of non-delirious patients*					
	0	1*	2	3*	4*	unknown
item 1	255 (99.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1 (0.4%)
item 2	157 (61.3%)	94 (36.7%)	3 (1.2%)	0 (0.0%)	-	2 (0.8%)
item 3	253 (98.8%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	-	2 (0.8%)
item 4	254 (99.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	2 (0.8%)
item 5	175 (68.4%)	78 (30.5%)	1 (0.4%)	0 (0.0%)	-	2 (0.8%)
item 6	93 (36.3%)	130 (50.8%)	17 (6.6%)	14 (5.5%)	0 (0.0%)	2 (0.8%)
item 7	0 (0.0%)	184 (71.9%)	71 (27.7%)	-	-	1 (0.4%)
item 8	72 (28.1%)	153 (59.8%)	29 (11.3%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
item 9	159 (62.1%)	91 (35.5%)	5 (2.0%)	0 (0.0%)	-	1 (0.4%)
item 10	251 (98.0%)	-	4 (1.6%)	-	0 (0.0%)	1 (0.4%)

** not all ratings are possible on all items(-)*

DRS-items	Ratings of delirious patients*					
	0	1*	2	3*	4*	unknown
item 1	13 (32.5%)	1 (2.5)%	0 (0.0%)	4 (35.0%)	-	12 (30%)
item 2	4 (10.0%)	11 (27.5%)	6 (15.0%)	7 (17.5%)	-	12 (30%)
item 3	19 (47.5%)	0 (0.0%)	8 (20.0%)	1 (2.5%)	-	12 (30%)
item 4	21 (52.5%)	1 (2.5%)	0 (0.0%)	6 (15.0%)	-	12 (30%)
item 5	6 (15.0%)	13 (32.5%)	6 (15.0%)	3 (7.5%)	-	12 (30%)
item 6	1 (2.5%)	7 (17.5%)	2 (5.0%)	16 (40.0%)	2 (5.0%)	12 (30%)
item 7	0 (0.0%)	11 (27.5%)	17 (42.5%)	-	-	12 (30%)
item 8	1 (2.5%)	11 (27.5%)	11 (27.5%)	5 (12.5%)	0 (0.0%)	12 (30%)
item 9	12 (30.0%)	6 (15.0%)	10 (25.0%)	0 (0.0%)	-	12 (30%)
item 10	14 (35.0%)	-	8 (20.0%)	-	6 (15.0%)	12 (30%)

Table 2
The frequency of the item-scores on the DRS max. for delirious patients (n=40)

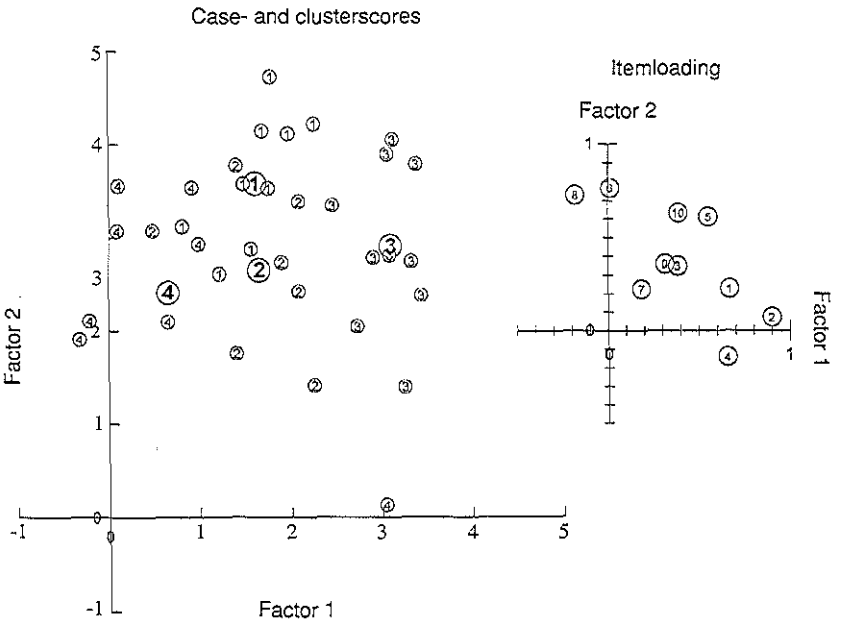
DRS-items	Ratings of delirious patients*					
	0	1*	2	3*	4*	unknown
item 1	5 (12.5%)	1 (2.5%)	0 (0.0%)	30 (75.0%)	-	4 (10%)
item 2	2 (5.0%)	8 (20.0%)	8 (20.0%)	18 (45.0%)	-	4 (10%)
item 3	18 (45.0%)	0 (0.0%)	16 (40.0%)	2 (5.0%)	-	4 (10%)
item 4	23 (57.5%)	0 (0.0%)	0 (0.0%)	13 (32.5%)	-	4 (10%)
item 5	1 (2.5%)	15 (37.5%)	12 (30.0%)	8 (20.0%)	-	4 (10%)
item 6	2 (5.0%)	3 (7.5%)	0 (0.0%)	25 (62.5%)	6 (15.0%)	4 (10%)
item 7	0 (0.0%)	6 (15.0%)	30 (75.0%)	-	-	4 (10%)
item 8	0 (0.0%)	5 (12.5%)	16 (40.0%)	14 (35.0%)	1 (2.5%)	4 (10%)
item 9	6 (15.0%)	12 (30.0%)	17 (42.5%)	1 (2.5%)	-	4 (10%)
item 10	4 (10.0%)	-	19 (47.5%)	-	13 (32.5%)	4 (10%)

** not all ratings are possible on all items (-)*

It is remarkable that not for all delirious patients the scores of the items "temporal onset" and "cognitive status" of the DRS max. were abnormal, since both are necessarily disturbed for a diagnosis of delirium according to the DSM-III-R criteria used. However, the item "cognitive status" of the DRS was rated using the MMSE, possibly being normal at the time of administering the DRS. The item "temporal onset" was sometimes rated as not being present in case of postoperative delirium of longer duration, incorrectly, since none of the patients had been delirious or psychotic, preoperatively. It also became clear that most delirious patients had no apparent delusions nor hallucinations, although almost all of them scored highly on perceptual disturbances, contrary to non-delirious patients on day 3. The cognitive status on day 3, postoperatively, of the delirious patients was more seriously disturbed than that of the non-delirious patients showing mainly very mild cognitive defects due to pain and/or emotional lability. (Almost) all delirious patients had psychomotor behaviour and sleep disturbances. Most of them showed lability of mood and variability of delirious symptoms. A majority of the non-delirious patients, not surprisingly, complained of sleep disturbances and a minority also experienced psychomotor behaviour problems and lability of mood.

The DRS max. item-scores for 36 delirious patients were correlated with each other using the Spearman rankorder correlation. Cognitive dysfunction correlated with psychomotor behaviour ($r=0.41$, $p=.014$), sleep-wake cycle disturbances ($r=0.39$, $p=.02$) and variability of symptoms ($r=0.38$, $p=.023$). In line with Trzepacz et al. [4], temporal onset of symptoms correlated well with per-

Figure 3
Loading of the items of the DRS max. on two identified factors and case- and clusterscores in relation to these factors



ceptual disturbances (r=0.53, p=.001). However, contrary to their findings this item did not correlate with lability of mood, but with psychomotor behaviour (r=0.50, p=.002) and variability of symptoms (r=.37, p=.028). Psychomotor behaviour further correlated well with perceptual disturbances (r=0.59, p<.001), sleep-wake cycle disturbances (r=0.39, p=.02), lability of mood (r=0.37, p=.027) and variability of symptoms (r=0.46, p=.005). Hallucination type and delusions only correlated with perceptual disturbances (r=.50, p=.002 and r=0.35, p=.036, respectively). Perceptual disturbances also correlated with variability of symptoms (r=.33, p=0.47) and mood lability with variability of symptoms (r=0.40, p=.013). Of all the items, only "physical disorder" and "sleep-wake cycle disturbance" did not correlate with the (corrected) item total-scores.

Factor analysis of the resulting correlation matrix yielded, after varimax rotation for maximizing the variance per factor, the following three underlying factors: factor 1) temporal onset of symptoms, perceptual disturbances, delusions and psychomotor behaviour; factor 2) psychomotor behaviour, cognitive dysfunction, sleep-wake cycle disturbances and variability of symptoms; and factor 3) physical disorder and the absence of lability of mood. This last factor, however, most probably is an artefact, since the patients scoring highly on this item were more severely ill and, therefore, emotional lability was often difficult to assess.
It is however important to realize that for a reliable factor analysis at least ten

patients per item are needed. Therefore, in this case, the results only concern this specific patient sample and cannot be generalized.

Cluster analysis identified four subgroups of delirious patients as presented in table 3. The different clusters were not associated with age, number of complications, length of hospital stay, mortality or any of the identified predictors (chapter 6).

However, cluster 3 appeared to be significantly associated with a higher DRS

Table 3

Ratings of subgroups of delirious patients by cluster analysis (n=36)*

DRS-items	Cluster 1 (n=10)					Cluster 2 (n=7)					Cluster 3 (n=11)					Cluster 4 (n=8)				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
item 1	1	0	0	9	-	1	0	0	6	-	0	0	0	11	-	3	1	0	4	-
item 2	0	1	6	3	-	0	2	1	4	-	0	0	1	10	-	2	5	0	1	-
item 3	0	0	9	1	-	7	0	0	0	-	3	0	7	1	-	8	0	0	0	-
item 4	10	0	0	0	-	7	0	0	0	-	0	0	0	11	-	6	0	0	2	-
item 5	0	5	2	3	-	0	1	6	0	-	0	3	3	5	-	1	6	1	0	-
item 6	0	1	0	7	2	2	0	0	5	0	0	1	0	7	3	0	1	0	6	1
item 7	0	2	8	-	-	0	2	5	-	-	0	1	10	-	-	0	1	7	-	-
item 8	0	0	4	5	1	0	2	4	1	0	0	1	6	4	0	0	2	2	4	-
item 9	1	3	6	0	-	1	3	3	0	-	0	4	6	1	-	4	2	2	0	-
item 10	0	-	6	-	4	0	-	4	-	3	0	-	5	-	6	4	-	4	-	0

** not all ratings are possible on all items (-)*

max. score ($p<.0001$), but not with the maximum dosage of haloperidol, possibly reflecting more severe delirium with psychotic symptoms as shown in table 3. The patients in cluster 4 seemed to be a subgroup of delirium without psychotic symptoms, although judged to be confused about external reality. In cluster 1 all patients had hallucinations, but no delusions. Clustering the delirious patients into three groups consequently joined cluster 1 and 2, followed by cluster 4 when the delirious patients were clustered into two groups. In figure 3 the case- and clusterscores are shown in relation to the two identified factors, factor 1 representing a "psychotic" dimension and factor 2 a "cognitive/emotional" dimension as the itemloadings on the two factors are indicating.

Mokken Scale Analysis of the DRS 3 of 271 patients (in 25 cases items of the DRS were missing) was performed to test the scalability of the DRS, after the items had been dichotomized (possible rating per item 0 or 1). The reliability of the DRS proved to be satisfactory ($\rho=.81$), a ρ of more than .70 being a mi-

Table 4
Mokken Scale Analysis of the Symptom Rating Scale for delirium (n=27)*

		Mean score per item	H_i
Delusions	(item 4)	0.02	55
Type of hallucinations	(item 3)	0.02	.71
Psychomotor behaviour	(item 5)	0.02	.66
Variability of symptoms	(item 10)	0.03	.71
Temporal onset	(item 1)	0.03	.75
Lability of mood	(item 9)	0.04	.56
Perceptual disturbances	(item 2)	0.04	.66
Sleep-wake cycle disturbance	(item 8)	0.14	.44
Cognitive status	(item 6)	0.16	.60
Coefficient of scalability H			.61
Coefficient of reliability Rho			.81

**item 7 was excluded from further calculations because it was a constant.*

nimum requirement and a ρ of over .80 being desirable.
The H_i coefficients (all >.40) and the H coefficient (.61) indicated a strong hierarchical scale. A higher value for Hi implies a better fit of the item in the scale. These results seemed to confirm the supposed hierarchical character of the DRS, implicating that each item is related to a certain severity of delirium and that the items may be summed to provide a consistent measure of severity of delirium.

DISCUSSION

The DRS was analyzed using different methods to look for underlying dimensions (factor analysis), subgroups of delirium (cluster analysis) and to test the scalability (Mokken Scale Analysis). The small overlap in the DRS scores of delirious and non-delirious patients indicated high discriminant validity. Contrary to the findings of Tzrepazc et al. cognitive dysfunction was not correlated with hallucination type nor with delusions, implicating that patients with psychotic features were not, necessarily, more cognitively disturbed as is often assumed [4].
In our opinion, the dimensions and clusters found both reflected different degrees of severity of delirium, the patients with mainly psychotic features as demonstrated by factor 1 and cluster 3 (followed by cluster 2 and 1), showing more severe delirium and a higher DRS max. score than the patients with mainly cognitive and emotional disturbances (as expressed in factor 2 and cluster 4). This supposed hierarchical character was confirmed by Mokken Scale Analysis.
A major problem proved to be the fact that the DRS is lacking the possibility

to assess non-communicative patients. Since about 25% of the delirious patients were not able to communicate during some time of delirium, the DRS scores are not always reflecting the presence nor the severity of delirium. Also, it was not possible to distinguish hypoactive from hyperactive delirious patients (both disturbances were rated on item 5) nor hypoalert from hyperalert patients (attentional abnormality was rated on item 6 as one of the cognitive disturbances) making it impossible to look for different clinical subtypes of delirium. Another drawback of the DRS is the fact that it is based on unstructured clinical assessment introducing observation bias and decreasing reliability.

Operationalizing the criteria used, structuring and standardizing the assessments, recording individual symptoms and including an observational part, as was done in the development of the Delirium Symptom Interview [1], will further refine research instruments and improve the reliability and generalizability of the results found.

ADDENDUM
THE SYMPTOM RATING SCALE FOR DELIRIUM (DRS) [4]

Item 1: Temporal onset of symptoms
This item addresses the time course over which symptoms appear; the maximum rating is for the most abrupt onset of symptoms - a common pattern for delirium. Dementia is usually more gradual in onset (Lipowski, 1982). Other psychiatric disorders, such as affective disorders, might be scored with 1 or 2 points on this item. Sometimes delirium can be chronic (e.g., in geriatric nursing home patients), and unfortunately only 1 or 2 points would be assessed in that situation.

0 = No significant change from longstanding behaviour, essentially a chronic or chronic-recurrent disorder.
1 = Gradual onset of symptoms, occurring within a 6-month period.
2 = Acute change in behaviour or personality occurring over a month.
3 = Abrupt change in behaviour, usually occurring over a 1- to 3-day period.

Item 2: Perceptual disturbances
This item rates most highly the extreme inability to perceive differences between internal and external reality, while intermittent misperceptions such as illusions are given 2 points. Depersonalization and derealization can be seen in other organic mental disorders like temporal lobe epilepsy, in severe depression, and in borderline personality disorder and thus are given only 1 point.

0 = None evident by history or observation.
1 = Feelings of depersonalization or derealization.
2 = Visual illusions or misperceptions including macropsia, micropsia; e.g., may urinate in wastebasket or mistake bedclothes for something else.
3 = Evidence that the patient is markedly confused about external reality; e.g.,

not discriminating between dreams and reality.

Item 3: Hallucination type

The presence of any type of hallucination is rated. Auditory hallucinations alone are rated with less weight because of their common occurrence in primary psychiatric disorders. Visual hallucinations are generally associated with organic mental syndromes, although not exclusively, and are given 2 points. Tactile hallucinations are classically described in delirium, particularly due to anticholinergic toxicity, and are given the most points.

0 = Hallucinations not present.
1 = Auditory hallucinations only.
2 = Visual hallucinations present by patient's history or inferred by observation, with or without auditory hallucinations.
3 = Tactile, olfactory, or gustatory hallucinations present with or without visual or auditory hallucinations.

Item 4: Delusions

Delusions can be present in many different psychiatric disorders, but tend to be better organized and more fixed in non-delirious disorders and thus are given less weight. Chronic fixed delusions are probably most prevalent in schizophrenic disorders. New delusions may indicate affective and schizophrenic disorders, dementia, or substance intoxication but should also alert the clinician to possible delirium and are given 2 points. Poorly formed delusions, often of a paranoid nature, are typical of delirium (Lipowski, 1980).

0 = Not present.
1 = Delusions are systematized, i.e., well-organized and persistent.
2 = Delusions are new and not part of a preexisting primary psychiatric disorder.
3 = Delusions are not well circumscribed; are transient, poorly organized, and mostly in response to misperceived environmental cues; e.g., are paranoid and involve persons who are in reality caregivers, loved ones, hospital staff, etc.

Item 5: Psychomotor behaviour

This item describes degrees of severity of altered psychomotor behaviour. Maximum points can be given for severe agitation or severe withdrawal to reflect either the hyperactive or the hypoactive variant of delirium (Lipowski, 1980).

0 = No significant retardation or agitation.
1 = Mild restlessness, tremulousness, or anxiety evident by observation and a change from patient's usual behaviour.
2 = Moderate agitation with pacing, removing i.v.'s, etc.
3 = Severe agitation, needs to be restrained, may be combative; or has significant withdrawal from the environment, but not due to major depression or schizophrenic catatonia.

Item 6: Cognitive status during formal testing

Information from the cognitive portion of a routine mental status examination is needed to rate this item. The maximum rating of 4 points is given for severe cognitive deficits while only 1 point is given for mild inattention which could be attributed to pain and fatigue seen in medically ill persons. Two points are given for a relatively isolated cognitive deficit, such as memory impairment, which could be due to dementia or organic amnestic syndrome as well as to early delirium.

0 = No cognitive deficits, or deficits which can be alternatively explained by lack of education or prior mental retardation.

1 = Very mild cognitive deficits which might be attributed to inattention due to acute pain, fatigue, depression, or anxiety associated with having a medical illness.

2 = Cognitive deficit largely in one major area tested, e.g., memory, but otherwise intact.

3 = Significant cognitive deficits which are diffuse, i.e., affecting many different areas tested; must include periods of disorientation in time or place at least once each 24-hr period; registration and/or recall are abnormal; concentration is reduced.

4 = Severe cognitive deficits, including motor or verbal perseverations, confabulations, disorientation to person, remote and recent memory deficits, and inability to co-operate with formal mental status testing.

Item 7: Physical disorder

Maximum points are given when a specific lesion or physiological disturbance can be temporally associated with the altered behavior. Dementias are often not found to have a specific underlying medical cause, while delirium usually has at least one identifiable physical cause (Trzepacz et al., 1985).

0 = None present or active.

1 = Presence of any physical disorder which might affect mental state.

2 = Specific drug, infection, metabolic, central nervous system lesion, or other medical problem which can be temporally implicated in causing the altered behaviour or mental status.

Item 8: Sleep-wake cycle disturbance

Disruption of the sleep-wake cycle is typical in delirium, with demented persons generally having significant sleep disturbances much later in their course (Lipowski, 1982). Severe delirium is on a continuum with stupor and coma, and persons with a resolving coma are likely to be delirious temporarily.

0 = Not present; awake and alert during the day, and sleeps without significant disruption at night.

1 = Occasional drowsiness during day and mild sleep continuity disturbance at night; may have nightmares but can readily distinguish from reality.

2 = Frequent napping and unable to sleep at night, constituting a significant disruption or a reversal of the usual sleep-wake cycle.

3 = Drowsiness prominent, difficulty staying alert during interview, loss of self-control over alertness and somnolence.

4 = Drifts into stuporous or comatose periods.

Item 9: Lability of mood

Rapid shifts in mood can occur in various organic mental syndromes, perhaps due to a disinhibition of one's normal control. The patient may be aware of this lack of emotional control and may behave inappropriately relative to the situation or to his/her thinking state, e.g., crying for no apparent reason.

Delirious patients may score points on any of these items depending upon the severity of the delirium and upon how their underlying psychological state "colours" their delirious presentation. Patients with borderline personality disorder might score 1 or 2 points on this item.

0 = Not present; mood stable.

1 = Affect/mood somewhat altered and changes over the course of hours; patient states that mood changes are not under self-control.

2 = Significant mood changes which are inappropriate to situation, including fear, anger, or tearfulness; rapid shifts of emotion, even over several minutes.

3 = Severe disinhibition of emotions, including temper outbursts, uncontrolled inappropriate laughter, or crying.

Item 10: Variability of symptoms

The hallmark of delirium is the waxing and waning of symptoms, which is given 4 points on this item. Demented as well as delirious patients, who become more confused at night when environmental cues are decreased, could score 2 points.

0 = Symptoms stable and mostly present during daytime.

2 = Symptoms worsen at night.

4 = Fluctuating intensity of symptoms, such that they wax and wane during a 24-hr period.

REFERENCES

1. Levkoff S, Liptzin B, Cleary P, Reilly CH, Evans D. Review of research instruments and techniques used to detect delirium. In: Miller NE, Lipowski ZJ (Eds.) Delirium. Advances in research and clinical practice. 1991; 3: 253-271.
2. Gottlieb GL, Johnson J, Wanich C, Sullivan E. Delirium in the medically ill elderly: Operationalizing the DSM-III criteria. In: Miller NE, Lipowski ZJ (Eds.) Delirium. Advances in research and clinical practice. 1991; 3: 181-196.
3. Levkoff S, Cleary P, Liptzin B, Evans D. Epidemiology of delirium: An overview of research issues and findings. In: Miller NE, Lipowski ZJ (Eds.) Delirium. Advances in research and clinical practice. 1991; 3: 149-167.
4. Trzepacz PT, Baker RW, Greenhouse J. A Symptom Rating Scale for Delirium. J Psychiat Res 1988; 23: 89-97.
5. Mokken RJ. A Theory and Procedure of Scale Analysis. The Hague, Mouton, 1971.
6. Mokken RJ. Lewis C. A Nonparametric approach to the Analysis of Dichotomous item responses. Applied Psychological Measurement. 1982; 6: 417-430.
7. Debets P. Brouwer E. User's manual: A program for Mokken Scale Analysis for polychotomous items (version 1.50). Groningen, 1989.
8. Molenaar IW, Sijtsma K. Mokken's approach to reliability estimation extended to multicategory items, Kwantitatieve Methoden. 1988; 9: 115-126.

Chapter 6

DELIRIUM FOLLOWING CARDIAC SURGERY: INCIDENCE AND PREDICTIVE FACTORS

R.C. van der Mast, W.W. van den Broek, D. Fekkes, L. Pepplinkhuizen, E.P. Krenning and F.H.J. Roest

INTRODUCTION

The actual incidence of delirium after cardiac surgery with CPB is unknown. The estimates vary considerably somewhere between 3% and 47%, even when taking only those studies into account in which delirium is more or less well defined and comparable to current criteria as described in chapter 2 [1].

Many attempts have been made to identify risk factors for postcardiotomy delirium such as demographic and psychosocial variables like age, gender and personality factors; illness variables like a history of myocardial infarction; preoperative variables like severity of illness, anxiety, the presence of brain damage and exposure to psychoactive drugs; intraoperative variables like time on cardiopulmonary bypass, hypothermia and mean blood pressure; and postoperative variables like severity of illness in the recovery room, sleep deprivation and low cardiac output [1,2]. Most of the results of the studies reporting on postoperative delirium after cardiac surgery are not comparable and it has not been possible to identify one strong risk factor consistently [1].
Although there have been (preliminary) reports on the increased risk of postoperative delirium associated with, preoperatively, markedly abnormal levels of sodium, potassium or glucose [3], and, postoperatively, with raised serum levels of anticholinergic drugs [4-6], cortisol and beta-endorphin [7,8] and decreased plasma tryptophan levels [9,10], almost nothing is known about possibly predictive biological parameters for postoperative delirium and mediating pathophysiological mechanisms.

In chapter 4 the aims, patients, research methods and instruments of this study are described and accounted for. In summary, we examined 296 patients undergoing elective cardiac surgery pre- and postoperatively to estimate, among others, the current incidence of delirium after (various types of) cardiac surgery and to determine possible preoperative predictors, in particular the role of reduced plasma tryptophan and altered plasma aminoacids in relation to a catabolic state.

METHODS

MATERIALS

Predictive variables included in the analyses were: age, gender, marital state, level of education, employment status, somatic and psychiatric history during the last five years, number of preoperative medical diagnoses, inclusion in the study as an in- or outpatient, a history of alcohol abuse and admission medications; type of surgery; preoperative scores on the Mini Mental State Examination (MMSE), the 30-item version of the General Health Questionnaire (GHQ), the Münchner Alcohol Test (MALT), the Daily Activity List (DAL) and the Profile of Mood States (POMS); laboratory test results including plasma amino acid concentrations (tryptophan -TRP-, leucine -LEU-, isoleucine -ILE-, tyrosine -TYR-, valine -VAL-, phenylalanine -PHE-, taurine -TAU-

methione-MET- and serine -SER-), thyroid function tests (T_3, rT_3, TSH), cortisol, sodium, potassium and glucose, (pre)albumin, folic acid and vitamin B1, B_6 and B_{12}. The molar ratio TRP:albumin, the plasma ratios of TRP, TYR, PHE, the ratio TAU: MET x SER and the ratio rT_3:T_3 were calculated (see chapter 4). Since, at this point, the purpose was to detect possible risk factors before surgery, intra- and postoperative variables were not included.

STATISTICAL ANALYSIS

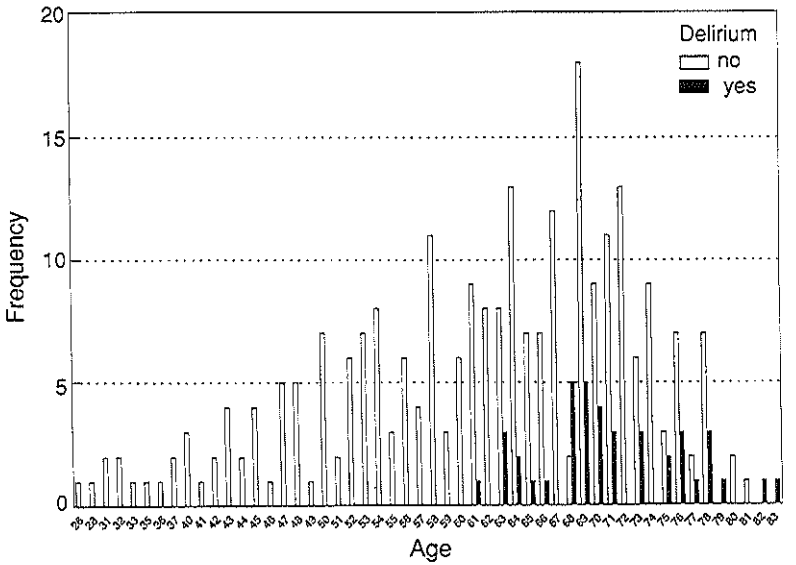
Independent sample t-tests for comparison of the means of continuous variables and X^2 -tests for comparison of proportions were used to assess a bivariate relationship with postoperative delirium. All tests were performed two-sided. To identify the factors independently associated with delirium bivariate correlates of delirium were entered in a backward stepwise logistic regression analysis with a significance level of .10 for entering. For this purpose, continuous variables were dichotomized at empirical cutpoints. Except for the MMSE, optimal cut-off points were found by calculating X^2 tests for increasing percentiles (10%/90%, 20%/80%.. etc.). Odds ratios, representing the odds of delirium in patients with a specific risk factor relative to the odds of delirium in patients without the risk factor, and their 95% confidence intervals (CI) were calculated. The ability of the model, resulting from logistic regression analysis, to discriminate between delirious and non-delirious patients was evaluated by Receiver Operating Characteristics (ROC) curve analysis [11], comparing the proportion correctly identified, delirious patients (true positive rate = sensitivity) with the proportion incorrectly identified, non-delirious patients (false positive rate = 1-specificity). A model with no predictive power would be a 45° line. The greater the predictive power, the more convex the curve. The area under the curve is used as a measure for predictive power. A model with no predictive power would have an area 0.5, a perfect model an area 1. A cut-off level was chosen which maximized the correct classification of delirious patients. Sensitivity and specificity at the resulting level were determined. To test the stability of the model, a bootstrap resampling procedure was applied [12]. A random sample of 50% of the cases in the study sample was drawn a 100 times. Each time a backward stepwise logistic regression analysis was performed on the variables in the model. The number of times a predictor was selected is an indication of the strength of that predictor [12]. A ROC curve was computed using the predicted probabilities of the selected (estimate) and non-selected (cross-over) cases, resprectively. The difference between the areas under both ROC curves is an indication of the shrinkage due to overfitting.

RESULTS

The sociodemographic characteristics of the overall sample are shown in table 1. The group studied included 192 (65 %) men and 104 (53 %) women. For both men and women the mean age was 63 (SD 10 and 13, respectively) years. The incidence of delirium, according to DSM-III-R criteria, appeared to be strongly associated with age. Under the age of 60 years delirium did not occur to increase subsequently with age (table 2 and figure 1).

Figure 1

Incidence of delirium after cardiac surgery: Age distribution of delirious (n=40) versus non-delirious patients (n=256).



The results of univariate analysis on all possible predictive variables for delirium after cardiac surgery are shown in table 3. Delirious patients were significantly older (mean age 71 years, SD 5.4) compared with non-delirious patients (mean age 61 years, SD 11.4).

Delirium was more common among patients included in the study as an inpatient, which might be an indication of severity of illness. Delirium was also associated with higher scores on the GHQ and the DAL, reflecting at first sight the presence of psychiatric symptoms and physical impairment, respectively. However, further analysis of the nature of the psychiatric symptoms scored on the GHQ revealed that delirious patients differed from non-delirious patients especially on the factor 'feelings of incompetence' ($t(291)=-1.74$, $p=.08$), probably reflecting, like the DAL, poor physical functioning more than psychopathology [13]. Patients with a MMSE-score < 24, suggestive of cognitive dysfunction, had higher rates of delirium. No differences were found between the scores on the (different subscales depression, anger, fatigue, vigour and tension of the) POMS of delirious and non-delirious patients.

Separately, the preoperative plasma concentrations of the aminoacids did not discriminate delirious from non-delirious patients. However, the PHE-ratio appeared to be significantly higher for the delirious group. Delirious patients also differed from non-delirious patients both in their serum concentrations of rT3 and their ratio rT_3:T_3, but not in the levels of T_3, TSH and cortisol.

Table 1
Sociodemographic characteristics of the overall population (n=296)

Mean age (SD)	63 (11)
Age range (years)	26-83
Gender	
Male	192 (65%)
Female	104 (35%)
Marital state/Living situation	
Married/Living together	235 (79%)
Unmarried/Living alone	61 (21%)
Education	
More than 12 years	29 (10%)
7-12 years	164 (55%)
6 years or less	101 (34%)
Unknown	2 (1%)
Employment	
Employed	50 (17%)
Retired	132 (45%)
Disabled	49 (17%)
Housewife	52 (18%)
Unemployed/Unknown	13 (3%)

Delirium was associated with a significantly lower mean albumin concentration and a decreased vitamin B1 level. There were no differences between delirious and non-delirious patients in the mean levels of sodium, potassium, glucose, prealbumin, folic acid or B12. We did not find markedly abnormal levels (defined as sodium <130 or >150 mmol/l, potassium < 3 or > 6 mmol/l or glucose < 3.3 or >16.7 mmol/l) to be very prevalent (n=4, n=4 and n=22, respectively) and, even if combined into one single variable, not related to the occurrence of delirium postoperatively, contrary to the findings of Marcantonio et al. [3].

Table 2
Incidence of delirium (n=296)

	Incidence		95% CI
Total population	40	(13.5%)	9.6-17.4%
Population < 60 years (n=96)	0	(0%)	0-3.8%
Population ≥ 60 years	40	(20%)	14.5-25.5%
60-64 years (n=50)	6	(12%)	5-24%
65-69 years (n=58)	12	(21%)	11-33%
70-74 years (n=58)	10	(17%)	9-29%
75+ years (n=34)	12	(35%)	20-54%

Table 3

Possible predictive variables for delirium (n=296)

	Non-delirious	Delirious	Test-value	p-value
Sociodemographic characteristics:				
Mean age (SD)	61.4 (11.3)	71.0 (5.4)	t(294)=-5.23	.000
Age ≥ 65 years	116 (45%)	34 (85%)	X^2(1)=21.80	.000
Gender:				
Male	167 (65%)	25 (63%)	X^2(1)=.11	.74
Female	89 (35%)	15 (38%)		
Marital state:				
Married etc.	201 (79%)	34 (85%)	X^2(1)=.89	.35
Living alone	55 (22%)	6 (15%)		
Education (years):				
> 12	26 (10%)	3 (8%)		
≤12 and > 6	143 (56%)	21 (53%)	X^2(2)=.78	.68
≤6	85 (34%)	16 (40%)		
Employment:				
Employed	47 (18%)	3 (8%)		
Retired	107 (42%)	25 (63%)		
Disabled	44 (17%)	5 (13%)	X^2(3)=5.88	.12
Housewife	45 (18%)	7 (18%)		
Unemployed	13 (5%)	0 (0%)		
Medical features:				
Somatic history:				
None	14 (65%)	1 (3%)		
Outpatient	23 (9%)	4 (10%)	X^2(3)=2.48	.48
1-2 admissions	177 (69%)	25 (63%)		
≥ 3 admissions	41 (16%)	10 (25%)		
Psychiatric history:				
None	233 (91%)	39 (98%)		
Outpatient	21 (8%)	1 (3%)	X^2(1)=1.66	.20
1-2 admissions	2 (1%)			
Number of diagnoses:				
1 diagnosis	57 (22%)	7 (18%)		
2 diagnoses	87 (34%)	15 (38%)	X^2(3)=.61	.89
3 diagnoses	73 (29%)	11 (28%)		
4 diagnoses	39 (15%)	7 (18%)		
Preoperative situation:				
Outpatient	151 (59%)	18 (45%)	X^2(1)=2.76	.096
Inpatient	105 (41%)	22 (55%)		
Alcohol consumption				
None	182 (71%)	28 (70%)		
Regular	73 (29%)	11 (28%)	X^2(1)=.003	.96
Abuse	1 (0%)	1 (3%)		
Admission medication:				
Nifedipine	42 (16%)	11 (28%)	X^2(1)=2.90	.089

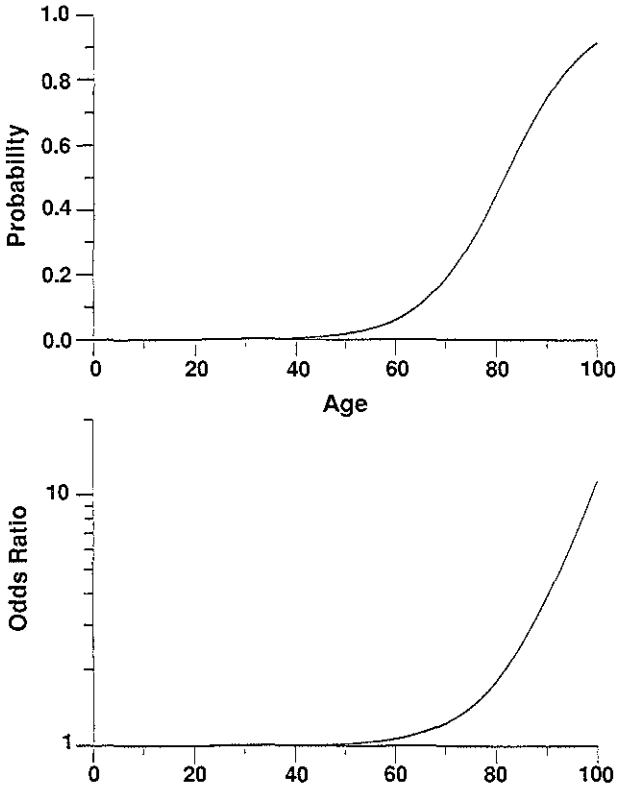
With regard to their sociodemographic characteristics delirious patients did not differ from non-delirious patients. Delirium was not associated with the number of preoperative medical diagnoses, nor with a more extensive somatic or psychiatric history during the last 5 years. The few patients reporting current or past alcohol abuse did not have higher rates of delirium. Also, none of the five patients having a score of more than 3 on the MALT, being suggestive of alcohol abuse, became delirious.

Table 3b

Possible predictive variables for delirium (n=296)

	Non-delirious	Delirious	Test-value	p-value
Test -scores:				
GHQ-30:				
Means (SD)	7.91(6.8)	10.00 (7.1)	t(294)=-1.80	.074
Score > 7	110 (43%)	24 (60%)	$X^2(1)=4.05$	.044
DAL:				
Means (SD)	4.79 (2.4)	5.15 (2.4)	t(294)=-.87	.38
Score > 6	58 (23%)	14 (35%)	$X^2(1)=2.86$	.090
MMSE:				
Means (SD)	27.55 (2.6)	27.18 (2.7)	t(293)=.84	.40
Score ≤ 23	19 (7%)	6 (15%)	$X^2(1)=2.77$	.096
MALT:				
Score >3	5 (2%)	0 (0%)	Fisher's Exact	1.0
POMS (means+SD):				
Depression	3.00 (4.4)	2.69 (4.4)	t(285)=.40	.69
Anger	2.06 (3.8)	1.44 (2.2)	t(284)=1.45	.15
Fatique	4.08 (5.0)	5.05 (5.5)	t(285)=-1.10	.27
Vigour	11.01 (4.0)	10.45 (4.6)	t(284)=.79	.43
Tension	7.30 (5.4)	6.18 (4.9)	t(285)=1.19	.24
Laboratory results:				
Animoacids (µmol/l, means+SD):				
TRP	40.53 (8.6)	38.28 (8.1)	t(294)=1.56	.12
LEU	124.60 (27.1)	120.45 (24.9)	t(294)=.91	.36
ILE	61.27 (13.7)	62.08 (13.2)	t(294)=-.34	.73
TYR	58.18 (14.5)	56.58 (12.4)	t(294)=.66	.51
VAL	217.17 (45.3)	205.65 (42.0)	t(294)=1.51	.13
PHE	54.60 (10.7)	56.73 (10.6)	t(294)=-1.17	.24
TAU	46.56 (17.8)	48.93 (11.0)	t(294)=-.82	.42
MET	21.15 (5.0)	20.65 (4.2)	t(294)=.59	.55
SER	99.18 (22.2)	95.58 (18.9)	t(294)=.97	.33
TRP-ratio	7.999 (1.68)	7.734 (1.63)	t(294)=.93	.35
TYR-ratio	11.751 (2.42)	11.888 (2.60)	t(294)=-.33	.74
PHE-ratio	10.983 (1.09)	11.895 (2.19)	t(294)=-2.52	.015
TAU: MET*SER	2.434 (1.09)	2.686 (1.04)	t(294)=-1.37	.17
Ratio TRP: albumin	0.067 (0.15)	0.066 (0.13)	t(288)=.53	.60
Thyroid function test (means+SD):	1.501 (.043)	1.451 (0.43)	t(294)=.69	.49
T_3 (nmol/l	0.252 (0.11)	0.288 (0.13)	t(294)=-1.83	.068
rT_3 (nmol/l)	1.732 (4.22)	1.324 (1.33)	t(294)=.61	.55
THS (mU/l)	0.176 (0.09)	0.212 (0.11)	t(294)=-2.33	.020
Ratio rT_3:T_3	524.0 (694.9)	530.4 (164.2)	t(294)=-.06	.96
Cortisol (nmol/l)				
Further laboratory results (means+ SD):	247.6 (66.2)	230.0 (51.5)	t(291)=1.61	.11
Prealbumin (mg/l)	41.39 (4.7)	39.65 (2.8)	t(288)=3.27	.002
Albumin (g/l)	141.0 (4.0)	140.8 (4.1)	t(292)=.25	.80
Sodium (mmol/l)	4.2 (0.6)	4.2 (0.5)	t(292)=-31	.76
Potassium (mmol/l)	10.6 (4.0)	10.3 (3.4)	t(261)=.40	.69
Glucose (mmol/l)				
Vitamins (nmol/l, means+SD):	561.0 (376.4)	616.2 (383.1)	t(294)=-.86	.39
Folic acid in ery's	103.6 (27.4)	94.8 (19.3)	t(264)=1.84	.066
B_1	60.86 (40.8)	49.53 (14.8)	t(266)=1.65	.101
B_6	312.4 (132.5)	294.4 (156.2)	t(289)=.78	.4

Figure 2
The probability and Odds Ratio of delirium in relation to age



Nifedipine, a calcium re-uptake inhibitor for treatment of angina pectoris that has been associated with anticholinergic effects in vitro [14], was the only medication used preoperatively that was associated with delirium. The number of patients taking medicines, usually associated with delirium, was too small to

Table 4
Incidence of delirium in relation to type of cardiac surgery (n=296)*

	Number of patients	Incidence	95% CI (%)
CABG	177 (59%)	13.6% (n=24)	8.5-18.6
VR	74 (25%)	9.5% (n=7)	3.9-18.5
CABG+VR	27 (9%)	22.2% (n=6)	8.6-42.3
OHO	22 (7%)	16.7% (n=3)	3.6-41.4

$*X^2(3)=2.94$, $p=.40$
CABG=coronary artery bypass graft; VR=valve replacement; OHO=other heart operations e.g. surgery for heart defects such as ventrical septal repair, with or without CABG and/or VR.

be able to detect a possible relationship between the occurrence of delirium and the preoperative use of, for example, anticholinergic compounds, benzodiazepines or corticosteroids [4-6,14,15]. The incidence of postoperative delirium in the four sub-samples, undergoing different types of cardiac surgery, was not significantly different, but the sample sizes of the patients undergoing CABG+VR and OHO were rather small as is reflected in the wide 95% CI's (table 4).

Age proved to be the main risk factor for postcardiotomy delirium (Odds Ratio = 1.14, 95% Confidence Interval: 1.08-1.2). The probability and Odds Ratio of postoperative delirium in relation to age are shown in figure in figure 2. Though 60 years appeared to be the optimal cut-off for dichotomizing patients in different categories, this was not possible since under the age of 60 years delirium did not occur. Therefore, 65 years, as the nearest cut-off point, was chosen (table 5).

Next to age, bivariate correlates of postcardiotomy delirium were: inclusion in the study as an inpatient, the preoperative use of nifedipine, a GHQ score > 7, a DAL-score > 6, and a MMSE score ≤ 24. Also, a low albumin concentration and both a high ratio rT_3:T_3 and PHE-ratio were correlates of delirium (table 5). The optimal cutoff for albumin appeared to be a plasma level of 41 g/l (cut-off at 40%), for the ratio rT_3:T_3 a value of .1450 (cut-off at 40%) and for the PHE ratio a value of 13.35 (cut-off at 90%).
The mean plasma concentration of Vitamin B1 and Vitamin B6 appeared to be lower for the delirious patients at p≤.1, but since there were too many missing data, these possible risk variables were not considered in the logistic regression analysis. All predictive variables, mentioned in table 5 were entered in a backward stepwise logistic regression analysis.

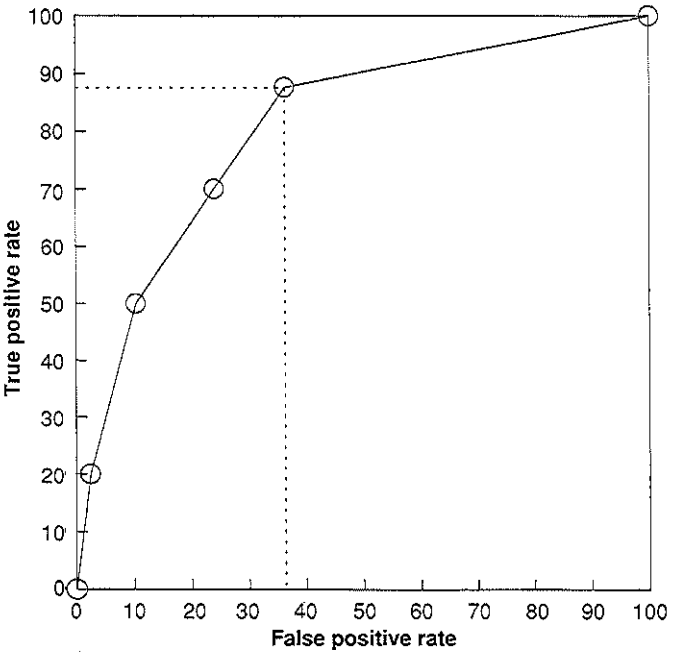
Tabel 5
Bivariate correlates of delirium after cardiac surgery (n=296)

Risk factor	Non-delirious n=256(%)	Delirious n=40(%)	Odds Ratio (95% CI)	p-value
Age ≥ 65 years	116(45%)	34(85%)	6.8(2.8-16.9)	<.001
Inclusion as an inpatient	105(41%)	22(55%)	1.8(.9-3.4)	.099
Use of nifedipine	42(16%)	11(28%)	1.9(.9-4.2)	.09
MMSE score ≤ 23	19(7%)	6(15%)	2.3(.8-6.1)	.10
GHQ score > 7	110(43%)	24(60%)	2.0(1.0-3.9)	.047
DAL score > 6	58(23%)	14(35%)	1.8(.9-3.8)	.094
Albumin ≤ 40 g/l*	90(36%)	28(70%)	4.1(2.0-8.6)	<.001
ratio rT_3:T_3 ≥ .1450**	145(57%)	31(78%)	2.6(1.2-5.8)	.015
PHE-ratio ≥ 13.35***	20(8%)	9(23%)	3.4(1.4-8.2)	.006

*$X^2(1)=16.5$, $p<.0001$ (optimal cut-off at 40%), **$X^2=6.3$, $p=.013$ (optimal cut-off at 40%), ***$X^2(1)=8.5$, $p=.004$ (optimal cut-off at 90%)*

Figure 3

ROC curve showing the proportion correctly identified, delirious patients (true positive rate) plotted against the proportion incorrectly identified, non-delirious patients (false positive rate) for the best discrimination set of predictive variables



The combination of predictive variables that resulted in the best discrimination between delirious and non-delirious patients consisted of age, the plasma level of albumin, the score on the GHQ, the value of the PHE ratio and the use of nifedipine (table 6). Based on this model, a ROC curve was calculated (figure 3) showing an area under the curve of 0.81 (Standard Error=.04), indicating predictive power. The predicted probability of delirium was calculated for each subject. At the cut-off level, which maximized the correct classification

Tabel 6

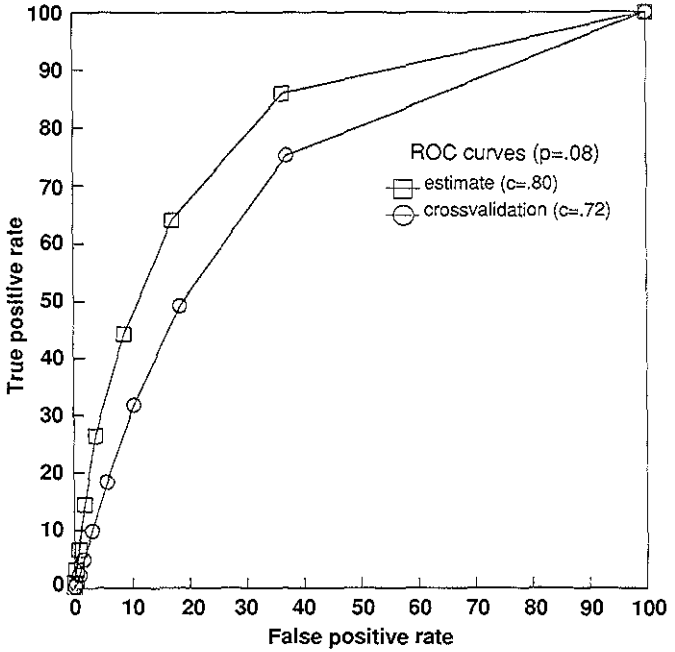
Predictors of delirium after cardiac surgery*

Predictor		Odds Ratio (95% CI)	p-value
y intercept	-1.59		
Age ≥ 65 years	1.65	5.2(2.1-13.3)	<.001
Albumin ≤ 40 g/l	1.25	3.5(1.6-7.6)	.002
Use of nifedipine	.89	2.4(1.0-5.8)	.047
PHE-ratio ≥ 13.35	.90	2.5(0.9-6.5)	.070
GHQ score > 7	.69	2.0(0.9-4.2)	.071

**Log likelihood=44.734, df=5, p<.0001*

Figure 4

ROC curves based on the selected sample (estimate) and the cross-over sample (crossvalidation)



of delirious patients (=.10), the percentage correctly identified, delirious patients (sensitivity), non-delirious patients (specificity) and overall classification were 88%, 64% and 70%, respectively.

The bootstrap resampling procedure showed that two variables, age and albumin concentration, were included in 89% and 74%, respectively, of the analyses. The variables score on the GHQ, the use of nifidipine and the PHE ratio met the criterion of being included at least in 30% of the analysis. The difference between the ROC curve based on the selected sample (area under curve .80, standard Error=.06) and the ROC curve based on the cross-over sample (area under curve .72, Standard Error=.06) was not significantly different (figure 4) meaning that the model seemed to be relatively stable.

The probability of delirium in relation to the number and kind of predictive variables is shown in table 7. The predicted probability of delirium in case of none of the risk factors being present was only 1.4%, increasing to almost 75% if all predictive variables were present. As was to be expected, patients with no risk factor proved to have a low rate of delirium (2.5%); patients with one risk factor had a rate of 10%, patients with 2 risk factors had a rate of 27.5% and patients with 3 or more risk factors had a rate of 60%.

DISCUSSION

The incidence of postoperative delirium among patients admitted to the thorax centre of the University Hospital Rotterdam for various types of cardiac

Table 7

The probability of delirium in relation to the number and kind of predictive variables (n=290)*

age ≥ 65 years	Albumin ≤ 40 g/l	PHE ratio ≥13.35	Use of nifedipine	GHQ>7	Predicted probability (%)	non-delirious	delirious (n=40)	total number of patients
0	0	0	0	0	1.4	35	1	36
0	0	0	0	yes	2.7	38	1	39
0	0	0	yes	0	3.2	11	1	12
0	yes	0	0	0	4.6	24	0	24
yes	0	0	0	0	6.7	30	2	32
0	0	0	yes	yes	6.2	7	0	7
0	0	yes	0	yes	6.3	4	0	4
0	yes	0	0	yes	8.7	10	0	10
0	yes	0	yes	0	10.5	1	2	3
0	yes	yes	0	0	10.6	2	0	2
yes	0	0	0	yes	12.5	18	2	20
yes	0	0	yes	0	14.9	3	2	5
yes	0	yes	0	0	15.1	3	0	3
yes	yes	0	0	0	20.1	25	5	30
0	0	yes	yes	yes	14.1	1	0	1
0	yes	0	yes	yes	18.8	2	1	3
0	yes	yes	0	yes	19.1	1	0	1
yes	0	0	yes	yes	25.7	6	1	7
yes	0	yes	0	yes	26.1	3	2	5
yes	0	yes	yes	0	30.1	1	0	1
yes	yes	0	0	yes	33.3	12	9	21
yes	yes	0	yes	0	37.9	4	2	6
yes	yes	yes	0	0	38.3	3	1	4
yes	yes	0	yes	yes	54.8	4	2	6
yes	yes	yes	0	yes	55.2	1	6	7
yes	yes	yes	yes	yes	74.9	1	0	1

**the number of patients do not add up to 296 because of missing values of albumin.*

surgery was 13.5%. Incidence rates for delirium after cardiac surgery reported in the literature (based on 16 adequate prospective studies, see chapter 2) vary from 3-47% [1]. In the 4 studies [16-19] finding an incidence rate lower than 13.5% -e.g. 6%, 12%, 7% and 3% respectively-, the mean age was not as high as in our study -54, 54, 59 and 54 versus 63 years respectively-, which may be an explanation for the higher incidence of delirium found in our study. However, in the 12 studies [4, 20-30] reporting a higher than 13.5% incidence (22-47%) the mean age was even lower varying from 39-55 years, age being no explanation for our lower incidence rate. These studies were mainly published in the earlier years and since only year of publication appeared to be significantly related to the incidence of delirium after cardiac surgery, the later publications show a tendency to a lower incidence, possibly due to improved

surgical and cardiopulmonary techniques [1]. This may explain the lower incidence rate found in our study. Moreover, our exclusion of patients presenting delirious symptoms only on the first day postoperatively, may have decreased the incidence somewhat.

Because in surgery for valvular repair the heart has to be opened more extensively with a possibly greater chance of cardiac damage, (micro)embolization and brain injury [25], another possible reason for the reported differences in incidence rates may be the kind of surgery [1]. Nevertheless, the incidence rates in patients undergoing different types of cardiac surgery were not significantly different and the kind of surgery did not appear to be a predictor for postoperative delirium.

Advanced age, as in many previous studies, proved to be a strong risk factor for delirium [1-3]. Age related changes in the brain, including a less functioning stress regulating system, alterations in neurotransmitter systems and increased vulnerability for, among others, the effects of hypoxia and thiamine deficiency (see chapter 3.1), seem to predispose elderly patients to delirium.

Also, cognitive dysfunction and alcohol abuse are well known for contributing to delirium [2,3,31]. Although in this study delirium appeared to be related to cognitive dysfunction, defined as a score on the MMSE ≤ 23, we did not find these variables to be predictive for delirium after cardiac surgery, possibly due to the small number of patients showing a low score on the MMSE or reporting alcohol abuse.

The combination of features that best discriminated between delirious and non-delirious patients consisted of, next to age, a plasma level of albumin ≤ 40 g/l, a score on the GHQ > 7, a PHE ratio ≥ 13.35 and the preoperative use of nifedipine. In this way 88% of the patients could be correctly classified as delirious and 64% as non-delirious. Testing the stability of this model, it proved to be relatively stable showing that age and plasma concentration of albumin were the srongest predictive factors for postoperative delirium.
There have been many studies surveying the relation of illness variables like somatic history, co-morbidity and severity of illness to delirium after cardiac surgery [2]. Most studies, using the New York Heart Association functional class, did find delirium to be associated with preoperative severity of illness [2]. Since we were interested in a more objective measure of severity of illness, we focused on the influence of a catabolic state and stress on the occurrence of delirium, as reflected in the level of (pre)albumin, the ratio rT_3:$T3_3$ and cortisol, apart from medical history variables and the scores on the GHQ and the DAL. Of all these 'illness' variables inclusion as an inpatient, a GHQ score > 7, A DAL score > 6, the ratio rT_3:$T3_3$ and the concentration of albumin were associated with postoperative delirium. The level of albumin and the GHQ score were independent predictors for delirium, meaning a more catabolic state and greater physical impairment respectively for delirious patients com-

pared with non-delirious patients.
Surprisingly, of all the admission medications nifedipine was the only one that proved to be a predictor for delirium. This may be due to its possibly anticholinergic activity, being a known risk factor for postoperative delirium [4-6,14,15], but may also indicate more serious preoperative illness, since generally first beta blockers and/or digoxin are prescribed first for treatment of angina pectoris.
Although abnormal laboratory values have often been associated with delirium [31], our finding that delirious patients did not differ from non-delirious patients in their mean serum concentrations of sodium, potassium and glucose is not surprising, since the patients studied were not admitted for an acute illness, but for an elective procedure for which they were carefully screened. In line with Marcantonio et al. [3], who studied delirium after non-cardiac surgery, we did not find markedly abnormal levels (defined as sodium <130 or >150 mmol/l, potassium < 3 or > 6 mmol/l or glucose < 3.3 or >16.7 mmol/l) to be very prevalent (n=4, n=4 and n=22, respectively) and, even if combined into one single variable, not related to the occurrence of delirium postoperatively, contrary to their findings. Nevertheless, the level of albumin was strongly associated with delirium, as was previously found in non-surgical, acutely ill delirious patients [32,33]. To our knowledge a reduced level of albumin has never been detected as a predictor for delirium in elective surgical, rather 'healthy' patients without any acute illnes. The reduced albumin concentration may reflect cachexia and a 'hidden' poor physical condition, resulting from malnutrition and/or non-nutritional factors such as certain disease states, and may lead to increased vulnerability as was also suggested from the scores on the DAL and the GHQ. Furthermore, hypoalbuminemia can contribute to the development of delirium as a side effect of certain highly albumin-bound drugs [33].
Since, consistent with the findings of McIntosh at al. [7], there was no difference in the mean preoperative levels of plasma cortisol between delirious and non-delirious patients, preoperative elevated stress did not seem to parallel the more catabolic state and poorer physical condition of delirious patients. However, one must keep in mind that a single measurement of cortisol concentration is most probably a too crude measure for evaluating physiological stress level.

We were interested in the preoperative aminoacid concentrations and their ratios because from a preliminary study it was suggested that delirium after cardiac surgery with cardiopulmonary bypass (CPB) may be related to reduced plasma tryptophan, due to a catabolic state and altered cerebral serotonin metabolism [9]. Moreover, several other neurotransmitter alterations and deficiencies have been hold responsible for the occurrence of (postcardiotomy) delirium, notably acetylcholine and noradrenaline .
Though the aminoacids separately, including TRP, did not discriminate between delirious and non-delirious patients, a high plasma ratio PHE:LEU+ILE+VAL+TYR+TRP was associated with delirium. Thus, our findings do not sup-

port the hypothesis that a preoperative reduced TRP availability from plasma plays a role in the etiology of postcardiotomy delirium, since both TRP and the ratio of TRP were not different for delirious and non-delirious patients. However, the combination of the levels of aminoacids, among which TRP and TYR, as included in a high ratio of PHE proved to be a predictor for delirium. Because of a particular affinity of the blood-brain barrier for PHE in preference of the other aminoacids [34], (relative) elevations of PHE as reflected in this ratio may block the uptake of the other neutral aminoacids such as TRP and, to a lesser extent TYR, into the brain. Moreover, both for delirious and non-delirious patients most of the preoperative aminoacid concentrations, except LEU, ILE, PHE, were already extremely low preoperatively, compared with normal controls. It is therefore possible that this plasma aminoacid imbalance has important consequences, as the organism may under stressful conditions no longer be able to maintain a, for an adequate neurotransmitter function, balanced influx of aminoacids into the brain. One may hypothesize that a decreased TRP availability, only in the presence of a (relatively) increased PHE, which has a much higher affinity for the bloodbrain barrier, is a possible risk factor.
Since the influx of PHE into the brain does not seem to be compromised, it may, as a precursor of (cerebral) TYR, compensate for the endangered cerebral NA and DA production. A diminished cerebral influx of TRP, however, may cause a decrease in serotoninergic function. This combination of, on the one hand, decreased serotoninergic and possibly cholinergic activity and, on the other hand, normal or increased noradrenergic and dopaminergic activity may play a complicated role in the occurrence of postcardiotomy delirium, making the patients, especially in the presence of other risk factors, more vulnerable for the stress and complications of surgery with CPB.

Concluding, elderly patients due to age related changes in the brain, in particular in the neurotransmitter and stress regulating system, already more vulnerable for stress induced alterations, being in a catabolic, poor physical condition and probably having an elevated anticholinergic plasma level, may be less able to compensate for imbalanced plasma aminoacid concentrations to maintain adequate neurotransmitter function in the brain under stressful circumstances, giving rise to a greater chance of postoperative delirium. Further research is needed to study the effect of preoperative interventions like restoration of a catabolic state, vitamin B shortage and aminoacid disturbances on the incidence of delirium among these high-risk, elderly patients.

REFERENCES

1. Mast RC van der, Roest FHJ. Delirium after cardiac surgery: A critical review. Submitted for publication.
2. Smith LW, Dimsdale JE. Postcardiotomy delirium: Conclusions after 25 years ? Am J Psychiatry 1989; 146: 452-458.
3. Marcantonio ER, Goldman L, Mangione CM, Ludwig LE, Muraca B, Haslauer CM, Donaldson MC, Whittemore AD, Sugarbaker DJ, Poss R, Haas S, Cook EF, Orav EJ, Lee TH.

A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994; 271: 134-139.
4. Tune LE, Damlouji NF, Holland A, et al: Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981; 2: 651-653.
5. Miller PS, Richardson JS, Christopher AJ, Lemay JS, Hiscock M, Keegan DL. Assocation of low serum anticholinergic levels and cognitive impairment in elderly presurgical patients. Am J Psychiatry 1988; 145: 342-345.
6. Golinger RC, Peet T, Tune LE. Association of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatry 1987; 144: 1218-1220.
7. McIntosh TK, Bush HL, Yeston NS et al. Beta-endorphin, cortisol and postoperative delirium: A preliminary report. Psychoneuroendocrinology 1985; 10: 303-313.
8. Naber D, Bullinger M. Neuroendocrine and psychological variables relating to postoperative psychosis after open-heart surgery. Psychoneuroendocrinology 1985; 10: 315-324.
9. Mast RC van der, Fekkes D, Moleman P, Pepplinkhuizen L. Is postoperative delirium related to reduced plasma tryptophan? The Lancet 1991; 338: 851-852.
10. Caston JC, Utley JR, Fleming HE. Endocrine marker for l-tryptophan response in cardiopulmonary bypass delirium patients: Case reports. Advances in Therapy 1989; 6: 161-179.
11. Hosmer DW, Lemeskow S. Applied logistic regression. New York, Wiley, 1989.
12. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: Application to the Cox regression model. Statistics in Medicine 1992; 11: 2093-2109.
13. Huppert FA, Eurof Walters D, Day NE, Elliott BJ. The factor structure of the General Health Questionnaire (GHQ-30). A reliability study on 6317 community residents. Brit J Psychiatry 1989; 155: 178-185.
14. Tune LE, Carr S, Hoag BS, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: Potential means for assessing risk of delirium. Am J Psychiatry 1992; 149: 1393-1394.
15. Tune LE, Bylsma FW. Benzodiazepine-induced and anticholinergic-induced delirium in the elderly. In: Miller Ne, Lipowski ZJ, Lebowitz BD (Eds) Delirium. Advances in research and clinical practice. International Psychogeriatrics 1991; 3: 397-408.
16. Sveinsson IS: Postoperative psychosis after heart surgery. J Thorac Cardiovasc Surg 1975; 70: 717-725.
17. Sadler PD: Incidence, degree, and duration of postcardiotomy delirium. Heart Lung 1981: 10: 1084-1091.
18. Calabrese JR, Skwerer RG, Gulledge AD, et al: Incidence of postoperative delirium following myocardial revascularization. Cleve Clin J Med 1987; 54: 29-32.
19. Carella F, Traviani G, Contri P, et al.: Cerebral complications of coronary by-pass surgery. A prospective study. Acta Neurol Scand 1988; 77: 158-163.
20. Egerton N, Kay JH: Psychological disturbance associated with open-heart surgery. Br J Psychiatry 1964; 110: 443-449.
21. Abram HS: Adaptation to open-heart surgery. A psychiatric study of response to the threat of death. Am J Psychiatry 1965; 122: 659-667.
22. Weiss SM: Psychological adjustment following open-heart surgery. J Nerv Ment Dis 1966; 143: 363-368.
23. Kimball CP: Psychological responses to the experience of open heart surgery. I. Am J Psychiatry 1969; 126: 96-107.
24. Heller SS, Frank KH, Malm JR, Bowman FO, Harris PD, Charlton MC, Kornfeld DS: Psychiatric complications to open-heart surgery. N Engl J Med 1970; 283: 1015-1020.
25. Tufo HM, Ostfeld AM, Shekelle R: Central nervous system dysfunction following open-heart surgery. JAMA 1970; 212: 1333-1340.
26. Kimball CP: The experience of open-heart surgery, 3: toward a definition and understanding of postcardiotomy delirium. Arch Gen Psychiatry 1972; 27: 57-63.
27. Kornfeld DS, Heller SS, Frank KA, Moskowitz R: Personality and psychological factors in postcardiotomy delirium. Arch Gen Psychiatry 1974; 31: 249-253.
28. Surman OS, Hackett TP, Silverberg EL, Behrendt DM: Usefulness of psychiatric intervention in patients undergoing cardiac surgery. Arch Gen Psychiatry 1974; 30: 830-835.
29. Kornfeld DS, Heller SS, Frank KA, Edie RN, Barsa J: Delirium after coronary artery bypass surgery. J Thorac Cardiovasc Surg 1978; 76: 93-96.
30. Summers WK: Psychiatric sequelae to cardiotomy. J Cardiovasc Surg 1979; 20: 471-475.
31. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990; 263: 1097-1101.
32. Trzepacz PT, Brenner R, Van Thiel DH. A psychiatric study of 247 liver transplantation can-

didates. Psychosomatics 1989; 30: 147-153.
33. Levkoff SE, Safran C, Cleary PD, Gallop J, Phillips RS. Identification of factors associated with the diagnosis of delirium in elderly hospitalized patients. JAGS 1988; 36: 1099-1104.
34. Richardson MA (Ed). Aminoacids in psychiatric disease. American Psychiatric Press, Washington, D.C. 1990.

Chapter 7

THE EFFECTS OF CARDIAC SURGERY WITH EXTRACORPOREAL BYPASS IN RELATION TO THE OCCURRENCE OF POSTOPERATIVE DELIRIUM

R.C. van der Mast, W.W. van den Broek, D. Fekkes, L. Pepplinkhuizen, E.P. Krenning and F.H.J. Roest

INTRODUCTION

Apart from preoperative factors, various intraoperative factors have been associated with delirium after cardiac surgery with extracorporeal circulation e.g. cardiopulmonary bypass (CPB). The main variables related to postoperative delirium were length of time on CPB, degree and duration of hypotension and hypothermia, kind and dosages of administered anaesthesia, the complexity of the surgical procedure and the presence of microemboli. However, different studies have found conflicting results concerning the contribution of these factors to the occurrence of delirium [1,2].

Cardiac surgery is a serious threat to the body and especially to the brain, due to the unusual physiology imposed by cardiopulmonary bypass (CPB) as was, for example, demonstrated from Magnetic Resonance Imaging showing brain swelling and reduction in size on the immediate postoperative scan in 6 patients having undergone coronary bypass surgery [3,4,5]. These cerebral abnormalities, supposed to be due to cytotoxic oedema induced by cerebral microemboli, hypoperfusion or haemodilution were not associated with neurologic or psychiatric disturbances. However, since only six patients were studied, these findings do not tell much about a possible relationship.

In chapter 3.3 possible pathophysiological mechanisms in the appearance of delirium after cardiac surgery with CPB were summarized concluding that delirium may be the result of a state of catabolism reflected in elevated levels of glucocorticoids and dopamine and a so-called "sick euthyroid syndrome" giving rise to alterations in plasma levels of the aminoacids and a generally decreased metabolism through reduced synthesis of ATP-, in combination with metabolic disturbances and cerebral hypoxia causing an imbalance of cerebral neurotransmission with a relative hyperactivity of the dopaminergic (noradrenergic and glutamate ?) system and hypoactivity of the cholinergic and serotoninergic system.

In this study pre-, intra- and postoperative variables were assessed to investigate the role of (reduced) cerebral tryptophan availability, changes in plasma concentrations of the other amino acids and a catabolic state on the occurrence of delirium in relation to cardiac surgery being a physiological stressful event.

METHODS (see also chapter 4)

In summary, duration of surgery, length of time on CPB, hypothermia time, lowest nasal temperature, minutes of mean systolic blood pressure ≤ 60 mm Hg. (generally considered the value below which cerebral hypoxia occurs) and medication during anaesthesia were recorded. On the first day postoperatively, 8.00 a.m., blood samples were drawn for plasma levels of cortisol, albumin, prealbumin, thyroid functions (T_3, rT_3, TSH) and the aminoacids. From 30 (of the 40) patients, the day after being diagnosed delirious, once again (fasting) blood samples were drawn, 8.00 a.m., for plasma levels of the amino-

acids, thyroid functions and cortisol (generally, on day 3 or 4 postoperotively). The molar ratio TRP:albumin, the plasma ratios of TRP, TYR, PHE, the ratio TAU:METxSER and the ratio rT_3:T_3 were calculated (see chapter 4).

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov goodness of fit test was executed to test on normal distribution of all continuous variables. Independent sample t-tests on all variables approximately normally distributed and, otherwise, Mann-Whitney tests were used to compare the means and mean ranks, respectively, of delirious and non-delirious patients. X^2-tests were done for comparison of proportions. All tests were performed two-sided. To evaluate the differences between delirious and non-delirious patients in their response to cardiac surgery, multivariate repeated measurement analysis of variance over preoperative and day 1 postoperative measurements of the plasma concentrations of the aminoacids and aminoacid ratios, the thyroid function tests and the ratio rT_3:T_3, cortisol and (pre)albumin were carried out, followed by univariate repeated measurement analysis of variance for individual variables. In subsequent analyses age, being an important independent risk factor for delirium, was entered as a covariate.

RESULTS

The surgical features of the delirious and non-delirious patients are shown in table 1. No significant differences were found in their intraoperative variables nor in the kind and dosage of medications used for anaesthesia.

Table 1

Surgical features of delirious (n=40) and non-delirious (n=256) patients

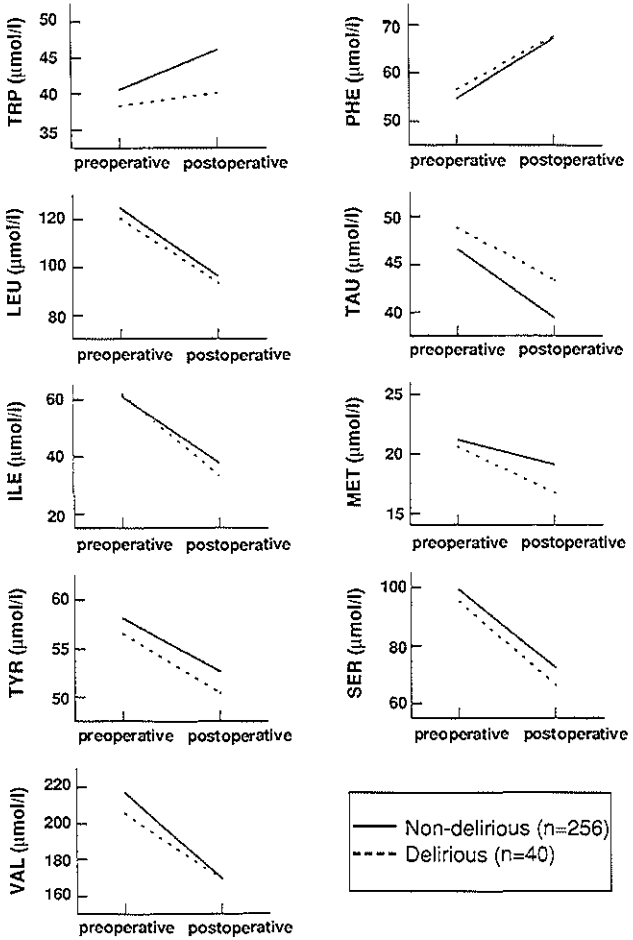
	Non-delirious	Delirious	All pts	Test-value	p-value
Time on CPB in min (median)	105	120	110	Z=-1.59	.11
Hypothermia in °C (median)	28	28	28	Z=-1.51	.13
Duration of hypothermia (median)	70	75	73	Z=-.30	.76
Hypotension (mean BP ≤ 60 Hg)					
No	51(20%)	13(33%)	64(22%)		
Yes	161(63%)	22(55%)	183(62%)	$X^2(2)$=3.34	.19
Unknown	44(17%)	5(13%)	49(17%		
Duration hypotension in min (SD)	35(27)	36(41)		t(179)=-.12	.90
Duration of surgery in min (median)*	240	265	240	Z=-1.48	.14

** Unknown for 6 and 1 patients respectively*

Under the influence of cardiac surgery with CPB most of the plasma levels of the aminoacids decreased significantly in relation to the already low levels preoperatively, for both delirious and non-delirious patients (MANOVA: F=100.66, df=286, p<.001). Only the plasma levels of TRP and PHE increased significantly (F=13.40, df=(1,294), p<.001; F=137.51, df=(1,294), p<.001, re-

Figure 1

Changes in plasma levels of the aminoacids for non-delirious (n=256) and delirious (n=40) patients under the influence of cardiac surgery



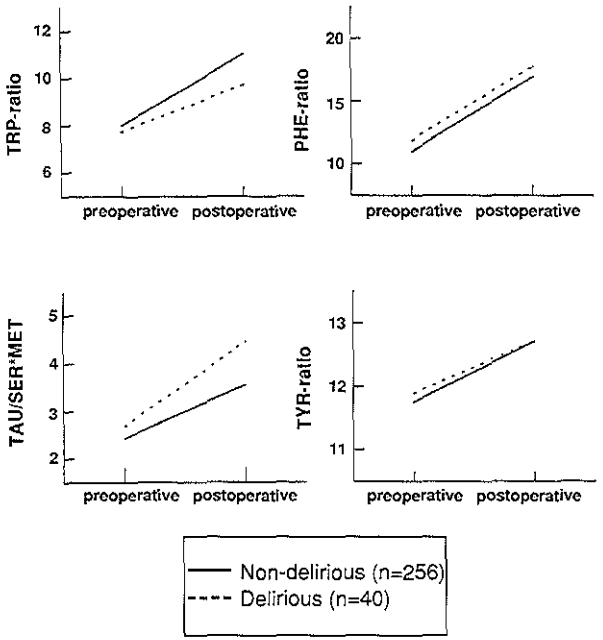
spectively) over time for all patients (see figure 1).

Multivariate repeated measurement analysis of variance showed a significant difference in the plasma aminoacid concentrations between delirious and non-delirious patients (F=2.76, df=286, p=.004), mainly caused by TRP (F=8.08, df=(1,294), p=.005). However, delirious patients did not respond differently to cardiac surgery (F=1.67, df=286, p=.096), meaning that the extent of change between the pre- and postoperative aminoacid concentrations was similar to that seen in non-delirious patients.

The plasma ratios of TRP, TYR, PHE, and the ratio TAU:METxSER appeared to increase significantly over time both for delirious and non-delirious patients (F=151.33, df=290, p<.001, figure 2). However, the increase in the ratio of

Figure 2

Changes in the plasma aminoacid ratios for non-delirious (n=256) and delirious (n=40) patients under the influence of cardiac surgery



TRP as a response to cardiac surgery was significantly less for the delirious group (F=5.72, df(1,294), p=.017). Delirium was associated with significantly different plasma aminoacid ratios (F=4.56, df=290, p=.001), due to differences in the ratios of TRP (F=6.62, df=(1,294), p=.011), PHE (F=5.30, df=(1,294), p=.005) and TAU:METxSER (F=7.91, df=(1,294), p=.022), but not with a significantly different response to cardiac surgery (F=1.67, df=290, p=.14), apart from the ratio of TRP.

Contrary to increasing total plasma TRP, the amount of free plasma TRP, as reflected in the molar ratio TRP:albumin, decreased over time, though not significantly (F=.30, df=(1,286), p=.59), for the delirious patients in contrast with a rise of both total and free TRP for the non-delirious group (figure 3). This may be due to the significantly lower level of albumin associated with delirium and, although both groups also differed significantly in their molar ratios TRP:albumin (F=3.92, df=(1,286), p=.049), their response to cardiac surgery concerning free TRP was not significantly different (F=3.21, df=(1,286), p=.074)

The levels of albumin, not surprisingly, increased significantly (F=83.77, df=(1,286), p<.001) for delirious and non-delirious patients, since they all received albumin and/or haemaccel during surgery. Although delirium was asso-

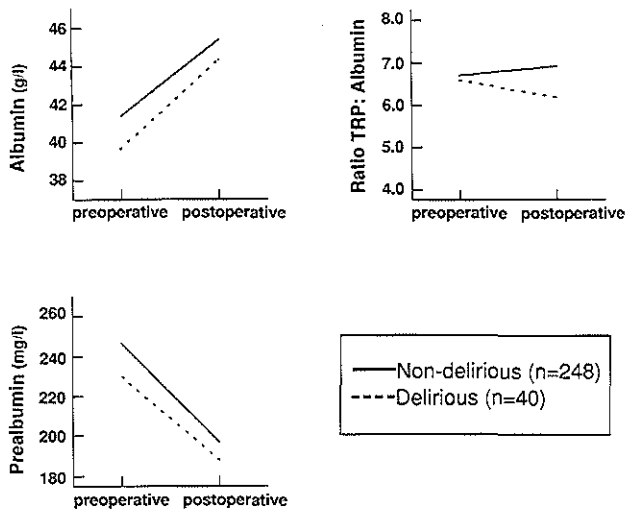
ciated with a lower albumin concentration -due the lower preoperative level-, no significant differences in response to cardiac surgery were found suggesting that both groups did get about the same amount of albumin during surgery. However, the prealbumin levels decreased significantly for both groups over time of surgery ($F=155.00$, $df=(1,284)$, $p<.001$) reflecting the catabolic circumstances of surgery, but not significantly different for delirious and non-delirious patients (figure 3).

In figure 4 the hormonal changes of delirious and non-delirious patients are shown. Over time, for all patients, the T_3 and TSH concentrations decreased and the rT_3 and cortisol levels increased significantly ($F=399.68$, $df=(1,294)$, $p<.001$; $F=9.53$, $df=(1,294)$, $p=.002$; $F=312.47$, $df(1,294)$, $p<.001$; and $F=7.12$, $df=(1,294)$, $p=.008$, respectively), giving an impression of the stressful nature of cardiac surgery. Also, the ratio rT_3:T_3 increased significantly for all patients ($p<.001$), the delirious patients being more catabolic as is shown by a, though not significantly, higher ratio rT_3:T_3 ($F=3.72$, $df=(1,293)$, $p=.055$). Nevertheless, they did not respond differently to cardiac surgery ($F=1.59$, $df=(1,293)$, $p=.21$).

The covariate analysis showed a significant effect of age on the aminoacid concentrations ($F=3.12$, $df=285$, $p=.001$). Although the multivariate tests for aminoacids was significant, mainly due to the influence of age on TRP and PHE, univariate analysis indicated that none of the aminoacids individually was significantly associated with age. The effect of age on the aminoacid ratios

Figure 3

Changes in the plasma levels of albumin and prealbumin, and molar ratio TRP:albumin for delirious (n=40) and non-delirious patients (n=248) under the influence of cardiac surgery



(F=5.08, df=289, p<.001) was mainly caused by the relation of age with the ratio of TRP (F=8.97, df=(1,293), p=.003). In figure 5 the aminoacid concentrations corresponding to age groups are shown.
Entering age as a covariate in the MANOVA for repeated measurements changed the above mentioned results as follows: Delirious and non-delirious patients no longer differed in their aminoacid concentrations (F=1.54, df=285, p=.13), except in the level of TRP (F=4.89, df=(1,293), p=.028). Nevertheless, delirium was still associated with significantly different aminoacid ratios (F=2.49, df=289, p=.032), mainly due to a significant higher ratio of PHE (F=5.01, df=(1,293), p=.026). Both groups no longer differed significantly in their molar ratio TRP: albumin.
Although covariate analysis showed a significant relation between age and the hormone concentrations (F=5.96, df=290, p<.001), especially T_3 (F=23.68, df=(1,293), p<.001), this finding did not alter the reported results essentially.

Figure 4

Changes in T_3, rT_3, TSH and cortisol concentrations, and the ratio rT_3:T_3 for delirious (n=40) and non-delirious patients (n=256) under the influence of cardiac surgery

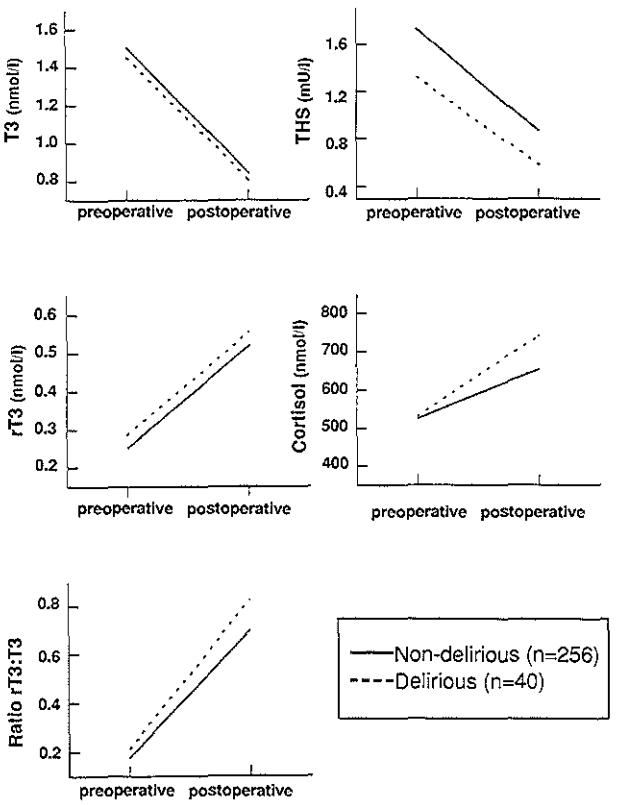
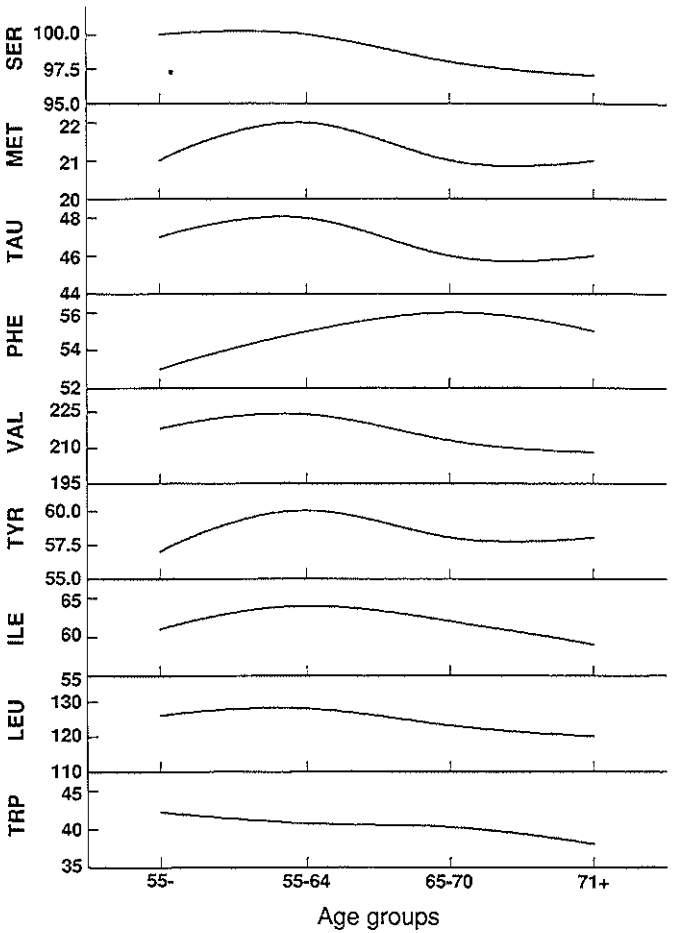


Figure 5
Amino acid concentration (μmol/l) in relation to age

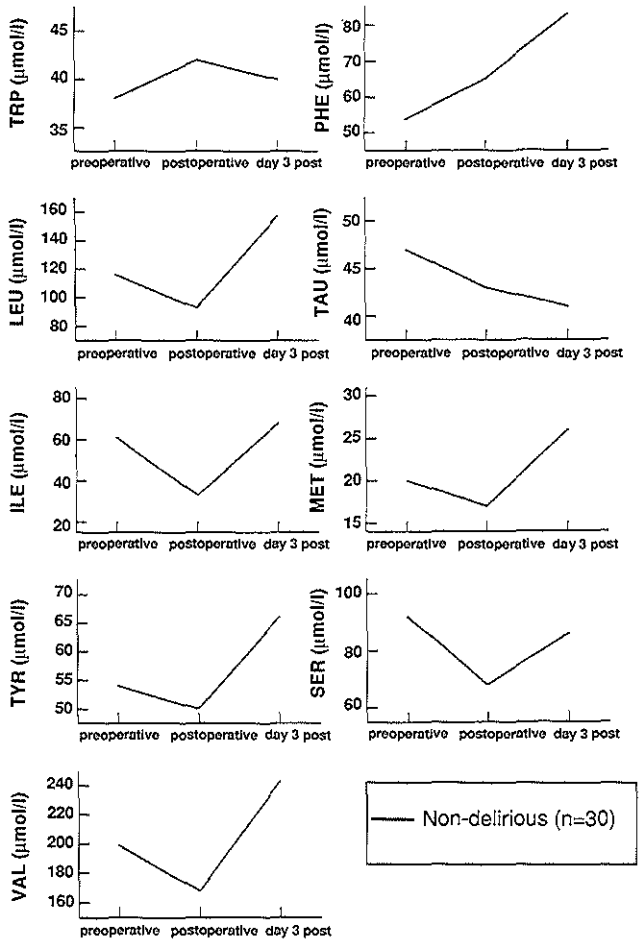


From 30 out of 40 patients who finally became delirious, once again blood samples were drawn after the diagnosis delirium was made (mostly on day 3 postoperatively). Although the results cannot be compared with the values of non-delirious patients, since these are missing, it is a remarkable finding that the mean level of TRP, after increasing under the influence of cardiac surgery, decreased to almost the preoperative low level (figure 6).

The levels of all the other amino acids, except TAU that further decreased, increased, often to levels (far) above the preoperative ones. The mean level of PHE, the aminoacid -next to TRP- that also increased over time of surgery, further increased in delirious patients to a far above normal value (> normal value plus 1 SD). The ratios of TRP, TYR, PHE and TAU:SERxMET all decreased (figure 7).

Figure 6

Changes in plasma levels of the aminoacids over time for delirious patients (n=30)



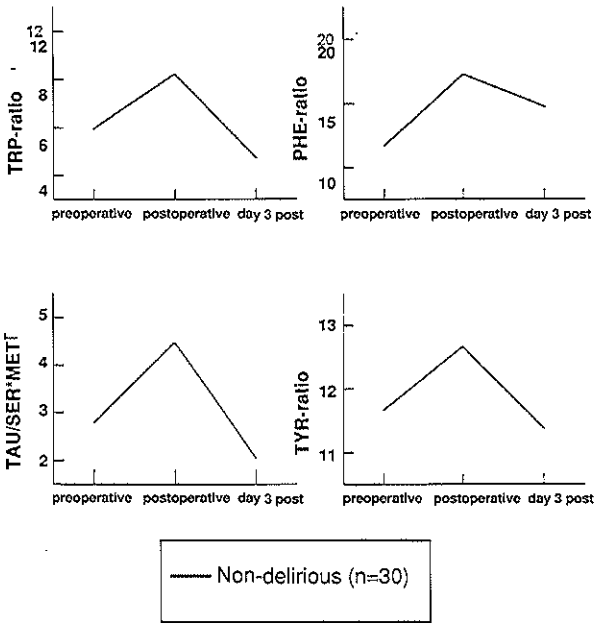
In figure 8 it is shown that for delirious patients, after day 1 postoperatively, the mean level of T_3, although still being below a normal value, slightly increased, but the level of rT_3 and, consequently, the ratio rT_3:T_3 further increased; the mean concentration of TSH increased to the preoperative level and the mean concentration of cortisol decreased.

DISCUSSION

Contrary to the findings reported in some earlier studies on delirium after cardiac surgery [6-8], postoperative delirium did not appear to be associated with intraoperative or anaesthesia variables. A possible explanation may be the shorter time on CPB and consequently shorter duration of hypothermia and surgery in this study, similar to that in other studies, finding no relation be-

Figure 7

Changes in the plasma amino acid ratios over time for delirious patients (n=30)



tween intraoperative variables and delirium [9-12].

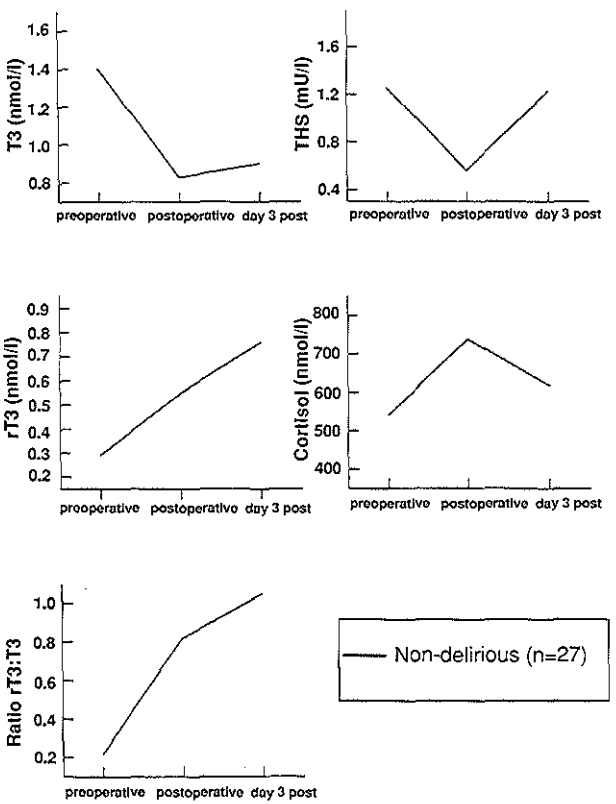
There was also no difference in the number of delirious and non-delirious patients undergoing periods of hypotension as was found by Sadler et al. [10]. Indeed, the blood pressure required for optimal cerebral perfusion is not known and hypoperfusion probably only plays a role in causing postoperative complications in already brain damaged patients with impaired cerebral autoregulation, leading to pressure dependent cerebral blood flow [5]. Since such patients were almost not present in our study sample, it is not surprising that hypotension was not associated with delirium.

In a preliminary study [13] it was hypothesized that reduced cerebral TRP availability from plasma played a role in postcardiotomy delirium due to a catabolic state, reducing TRP transport across the blood-brain barrier because of two important mechanisms: 1) the plasma concentration of the amino acids VAL, ILE, LEU, TYR and PHE, which compete with TRP for the transport-carrier at the blood-brain barrier, is increased due to degradation of muscle proteins; and 2) the plasma concentration of TRP is reduced because of induction of TRP pyrrolase by cortisol [14,15]. On the other hand it was suggested from animal research that stress decreased the plasma levels of the aminoacids, except of free TRP, in favour of the brain levels through altered blood-brain transport kinetics caused by stress provoked hormonal changes [16].

Contrary to our expectations, the mean plasma concentration of TRP in-

creased and those of the other neutral aminoacids, except PHE, reduced over time, resulting in a rise of the ratios of TRP and PHE, postoperatively.
The decrease of the plasma levels of almost all aminoacids, except TRP and PHE, may be in favour of the brain levels of these aminoacids [16]. The rise in the plasma concentrations of TRP and PHE may be the result of the decreased conversion of these aminoacids in their metabolites. The converting enzymes TRP hydroxylase in the liver and serotoninergic neurons and PHE hydroxylase in the liver, pancreas and kidney are in need of both oxygen and tetrahydrobiopterin, which is synthesized from GTP, for their activity [17]. The existence of a low T_3 syndrome causes a reduced synthesis of ATP and thus of GTP. The resulting decrease in tetrahydrobiopterin synthesis may, together with a diminished rate of metabolic processes in the liver due to the hypothermia and hypoxia, possibly lead to the decreased conversion and increased plasma levels of both TRP and PHE. Moreover, a deficient tetrahydrobiopterin supply leading to diminished conversion of cerebral TRP may directly affect the synthesis of serotonin in the brain.

Figure 8
Changes in T_3, rT_3, TSH and cortisol concentrations over time for delirious patients (n=27)



Nevertheless, delirium appeared to be especially associated with a lower plasma level of TRP (and a lower TRP ratio) and the increase in TRP ratio over time proved to be significantly less for delirious patients, supporting the hypothesis that a relationship between a reduced cerebral TRP availability from plasma and the occurrence of postoperative delirium may exist [13].

Furthermore, it is probably of great importance that for all patients the levels of the aminoacids TRP, TYR, MET and SER were, already preoperatively, below normal values (< normal value minus 1 SD) indicating decreased intake and/or a catabolic state. Delirious patients, being more catabolic as reflected in a lower mean concentration of albumin and a higher ratio rT_3:T_3, may have been less able to compensate for the inadequate preoperative TRP levels, since the main difference between delirious and non-delirious patients was a lower plasma level of TRP (and TRP ratio without age as covariate) and a smaller increase of TRP ratio in response to cardiac surgery. This inadequate compensation capacity may be due to the coexistence of a higher ratio of PHE in delirious patients, already found preoperatively, giving rise to an even more reduced cerebral availability of TRP, since the particular affinity of the blood-brain barrier for PHE in preference of the other aminoacids may cause a blockade of the uptake of the other neutral aminoacids such as TRP and, to a lesser extent TYR, into the brain. This may hamper adequate function of, especially the serotoninergic, neurotransmitter systems. The normal plasma levels of PHE, being a precursor of TYR, may take care of an adequate or, in the presence of an increased ratio of PHE, (relatively) elevated cerebral dopaminergic and noradrenergic function. Also, the finding that in delirious patients after the onset of delirium, the concentration of TRP (and the TRP ratio), in contrast to the normalized concentrations of all the other aminoacids, declined again, and that the concentration of PHE further increased, pointed in the direction of reduced cerebral availability of TRP -and consequently inadequate function of the serotoninergic neurotransmitter system- in delirium [13].

The association of delirium with a higher ratio TAU:SERxMET indicating lower plasma levels of the methyl donors SER and MET, may signify an endangered production of cerebral acetylcholine due to a lack of these methyl precursors. Moreover, this may also lead to increased levels of dopamin and (nor)adrenaline, since the enzyme cathechol-O-methyl-transferase (COMT) needs S-adenyl-methione (SAM), thus a methyl donor, for degradation of dopamin and (nor)adrenaline.

The increase in albumin concentration for both delirious and non-delirious patients is not very surprising since, during surgery, all patients received albumin and blood substitute transfusions keeping blood at a constant haematocrit value of 20 mmol/l during CPB, but still a significant lower level of albumin is associated with delirium, due to the much lower preoperative level.
Since the rise in albumin concentration was not different for both groups one may assume that they received the same amount of albumin during surgery.

In line with the findings of Naber et al. [18], studying 23 male patients undergoing cardiac surgery for aortic valve replacement, serum levels of cortisol (beta-endorphin and norepinephrin) increased dramatically not only for delirious but for all patients in the immediate postoperative period, demonstrating the stressful nature of this major operation. Also, the circadian rhythm with elevated levels of cortisol in the morning appeared not to be apparent before the fourth day postoperatively for all patients [18]. This is contrary to the results on seven patients undergoing elective non-cardiac surgery reported by McIntosh et al., who did find a significant relationship between delirium (n=3) and both increased levels of cortisol (and beta-endorphin) and a disrupted circadian rhythm [19]. It is of course possible that a more sophisticated method of measuring cortisol like post-dexamethasone cortisol levels or repeated measurements for a longer pre- and postoperative period, as was done by McIntosh, would have yielded different results, indeed discriminating delirious and non-delirious patients according to their cortisol and thus stress level. Since no significant differences between delirious and non-delirious patients were found in their cortisol levels, a stronger induction of the enzyme TRP pyrrolase in delirious patients cannot be hold responsible for the significant lower level of TRP in delirious patients. Furthermore, hypothermia probably causes enzymatic reactions in the liver to slow down, thus inhibiting the conversion of TRP (and PHE) in the liver.
For both delirious and non-delirious patients a significant decrease of TSH was found within one day postoperatively, paralleling the decrease in serum T_3 concentration, in contrast with the findings of Naber et al. [18] who reported unaffected serum levels of TSH, immediate postoperatively, followed by an increase after 2-3 days. This decline in TSH may be the result of the inhibiting effect of cortisol on the release of TRH and thus on TSH, preventing stimulation of the thyroid and maintaining a sick euthyroid syndrome.

After the onset of delirium, the thyroid functions and the concentration of cortisol still reflected the catabolic and stressful state of the delirious patients, with a tendency to recovery. Since data of non-delirious patients are missing, it remains unclear if, at this point, delirious patients are more catabolic and stressed compared to non-delirious patients.

Furthermore, next to changes in neurotransmitter function due to abnormalities in aminoacid concentrations e.g. TRP and PHE, the synthesis of various neurotransmitters is altered in relation to age, cerebral hypoxic hypoxia, anaemic hypoxia and thiamine deficiency, conditions also associated with (postoperative) delirium (see chapter 3.1). In animal research these circumstances have been associated with an excess of extracellular cerebral dopamine and glutamate, neurotransmitters being implicated in cellular damage and some features of delirium. The decline in cerebral cholinergic activity, occurring in relation to advanced age, hypoxia and substrate- and thiamine deficiency, may also play an important role in the occurrence of delirium, next to possible blockade of cholinergic transmission by the use of anticholinergic medications.

In conclusion, the findings of this study supported the hypothesis that reduced cerebral TRP availability, due to, already preoperatively, low levels of TRP combined with a high PHE ratio, plays a role in the occurrence of delirium after cardiac surgery, together with a shortage of the methyl donors SER and MET. Consequently, an imbalance of cerebral neurotransmission constituting a decreased serotoninergic -probably exacerbated through decreased conversion of cerebral TRP into serotonin due to diminished tetrahydrobiopterin synthesis- and cholinergic neurotransmission function on the one hand and a (relatively) increased activity of the dopaminergic (and noradrenergic) system, on the other hand, may underlie the occurrence of delirium after cardiac surgery.

Therefore, preoperative restoration of a catabolic state e.g. albumin level and the aminoacid concentrations and optimizing the physical condition of the patient undergoing cardiac surgery may decrease the occurrence of postoperative delirium.

REFERENCES

1. Smith LW, Dimsdale JE. Postcardiotomy Deliriun: Conclusions after 25 Years? Am J Psychiatry 1989; 146: 452-458.
2. Mast RC van der, Roest FHJ. Delirium after cardiac surgery: A critical review. Submitted for publication.
3. Clark RE. Cardiopulmonary bypass and thyroid hormone metabolism. In: Clark RE (Ed.). The acute cardiovascular actions of thyroid hormone. Ann Thorac Surg 1993; 56 (supplement): 35-42.
4. Harris DNF, Baily SM, Smith PLC, Taylor KM, Oatridge A, Bydder GM. Brain swelling in the first hour after coronary artery bypass surgery. The Lancet 1993; 342: 586-587.
5. Gilston A. Brain damage after cardiac surgery (Letter to the Editor). The Lancet 1986; 335: 1323.
6. Weiss SM: Psychological adjustment following open-heart surgery. J Nerv Ment Dis 1966; 143: 363-368.
7. Heller SS, Frank KH, Malm JR, Bowman FO, Harris PD, Charlton MC, Kornfeld DS: Psychiatric complications to open-heart surgery. N Engl J Med 1970; 283: 1015-1020.
8. Kornfeld DS, Heller SS, Frank KA, Moskowitz R: Personality and psychological factors in postcardiotomy delirium. Arch Gen Psychiatry 1974; 31: 249-253.
9. Kornfeld DS, Heller SS, Frank KA, Edie RN, Barsa J: Delirium after coronary artery bypass surgery. J Thorac Cardiovasc Surg 1978; 76: 93-96.
10. Sadler PD: Incidence, degree, and duration of postcardiotomy delirium. Heart Lung 1981: 10: 1084-1091.
11. Sveinsson IS: Postoperative psychosis after heart surgery. J Thorac Cardiovasc Surg 1975; 70: 717-725.
12. Calabrese JR, Skwerer RG, Gulledge AD, Gill CG, Mullen JD, Rodgers DA, Taylor PC, Golding LA, Lytle BW, Cosgrove DM, Bazarel MG, Loop FD: Incidence of postoperative delirium following myocardial revascularization. Cleve Clin J Med 1987; 54: 29-32.
13. Mast RC vd, Fekkes D, Moleman P, Pepplinkhuizen L. Is postoperative delirium related to reduced plasmatryptophan ? Lancet 1991; 338: 851-852.
14. Fernström JD, Wurtman RJ. Brain serotonin content: Physiological regulation by plasma neutral amino acids. Science 1972; 178: 414-416.
15. Lehman J.. Tryptophan deficiency stupor: A new psychiatric syndrome. Acta Psychiatr Scand 1982; suppl 300: 1-46.
16. Richardson MA (Ed). Amino acids in psychiatric disease. American Psychiatric Press, Washington, D.C. 1990.
17. Siegel G, Agranoff B, Albers RW, Molinoff P. Basic Neurochemistry. American Society for Neurochemistry, Raven Press, NY, 1989.
18. Naber D, Bullinger M. Neuroendocrine and psychological variables relating to post-opera-

tive psychosis after open-heart surgery. Psychoneuroendocrinology 1985; 10: 315-324.
19. McIntosh TK, Bush HL, Yeston NS et al. Beta-endorphin, cortisol and postoperative delirium: A preliminary report. Psychoneuroendocrinology 1985; 10: 303-313.

Chapter 8

CLINICAL COURSE AND OUTCOME OF DELIRIUM AFTER CARDIAC SURGERY

R.C. van der Mast, W.W. van den Broek, F.H.J. Roest

INTRODUCTION

In general, delirium is considered an indicator of grave prognosis. Indeed, in many studies delirium was found to be associated with higher morbidity and mortality rates, prolonged hospital stay, increased institutionalization and poor functional recovery [1-9].
The complication rates found in two studies investigating postoperative delirium among patients undergoing non-cardiac surgery were 54% and 15% for delirious patients compared to 15% and 2%, respectively, for non-delirious patients [4,7].

In a number of studies examining (elderly) general medical, non-cardiac surgical and mixed patient samples, mean length of hospital stay ranged between 12 and 24 days for patients with delirium compared to 7 and 14 days for non-delirious controls [2-5,7]. However, the relationship between delirium and duration of hospital stay remains unclear, since the results were not adjusted for age nor for severity of illness or complexity of surgical procedure, advanced age and serious illness being generally associated with longterm hospital treatment.

Delirious patients are, compared with patient control groups, more at risk for both in-hospital and post-discharge death. Different mortality rates probably reflect differing ages and other selection variables like the patients studied, acuteness of illness or surgery, severity of illness etc. [2,6,10]. In two prospective studies on delirium among patients admitted to a medical ward because of an acute illness, the in-hospital mortality rates were 8% and 65% for patients with delirium compared to 1% and 13.5%, respectively, for non-delirious unmatched hospital controls [2,3]. In a retrospective study on delirium among patients aged 60 years and over, admitted to both medical and surgical departments, including cardiac surgery, Levkoff et al. [5] reported a mortality of 13% for delirious patients compared to 5% for a non-delirious control group, matched according to admitting service. In patients with postoperative delirium following elective non-cardiac surgery a mortality of 4% was found compared with a 0.3% mortality rate in patients who did not develop delirium [7]. Though in the DSM-III-R death is mentioned as one of the sequelae of delirium, the higher mortality rate in delirious patients appeared to depend more on the medical condition than on the presence of delirium [2,3,6,7]. To our knowledge, until now no studies have examined morbidity and mortality rates in association with delirium after cardiac surgery. In this chapter course, including onset, severity and duration of, delirium will be described and outcome measures such as kind and number of complications, length of stay, in-hospital and six months post-discharge mortality rate and functional recovery will be examined.

METHODS

In chapter 4 the methods and instruments for assessing course and outcome in relation to delirium after cardiac surgery have been described. In summary,

the presence and severity of postoperative delirium were assessed using DSM-III-R criteria and the maximum scores on the Delirium Rating Scale (DRS), respectively. The assessment of the cognitive status, which is an item of the DRS, was done using the Mini Mental State Examination (MMSE). Based on clinical judgement, delirious patients were divided in three groups: 1. mild delirium, 2. moderate to severe delirium and, in case of impossible communication as a consequence of (prolonged) intubation and/or sedation, 3. probable delirium (though formally not assessable). The use of haloperidol medication was evaluated. Both delirious and non-delirious patients were followed during hospitalization to compare postoperative complications, medications, length of hospital stay, mortality and living situation after discharge. Six months after discharge all patients were interviewed by telephone to gather information about survival, living situation and physical impairment.

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov goodness of fit test was executed to test on normal distribution of all continuous variables. On all variables being approximately

Table 1

Outcome for non-delirious (n=256) and delirious (n=40) patients

Outcome	Non-delirious	Delirious	All patients	Test-value	p-value
Complications					
none or 1	173(68%)	6(15%)	179(61%)		
2-3	77(30%)	19(48%)	96(32%)	$X^2(2)=79.31$	<.001
4 or more	6(2%)	15(38%)	21(7%)		
Length of stay*					
median	11	14	11	Z=-3.49	<.001
mean	13	17	14		
In-hospital deaths	0(0%)	4(10%)	4(1.4%)	**	**
After discharge death (within 6 months)***	1(0.4%)	3(7.5%)	4(1.4%)	OR(95% CI)= 21(2-206)	.009
Total deaths within 6 months after surgery	1(0.4%)	7(17.5%)	8(2.8%)	OR(95% CI)= 54(7-461)	<.001
Discharge to ****					
Home	235(95%)	29(71%)	264(93%)	$X^2(1)=7.74$	.005
Longterm care	12(5%)	6(19%)	18(6%)	OR(95% CI)= 4(1-12)	.009

* *The number of days from the day before surgery to the day of discharge; 8 patients were discharged early (within 6 days postoperatively) to another hospital for normal further postoperative care and 4 in-hospital deaths were excluded.*

** *All in-hospital deaths were patients with delirium.*

*** *Number of patients is 278 because of 4 in-hospital deaths and 14 missing follow-up data .*

**** *Number of patients is 282 because of 4 in-hospital deaths, 8 early discharged patients and 2 missing values; Longterm care includes rehabilitive facility, nursing home, and other hospital or other department of own hospital for extended aftercare due to complications.*

normally distributed independent sample t-tests, otherwise Mann-Whitney-U tests, were used to compare the means and mean ranks, respectively, of delirious and non-delirious patients. X^2 and Fisher's exact tests were done for comparison of proportions. All tests were performed two-sided. Complication rates, lengths of hospital stay, mortality rates, and odds ratios and their confidence intervals were calculated. The Sign test was done to examine functional recovery at six months follow-up, as measured by the score on the DAL, compared with the preoperative functional status. Characteristics of delirium and patients who died are described.

RESULTS

In table 1 the outcome for delirious and non-delirious patients is shown. Delirium was associated with significant more complications ($p<.001$), occurring during the entire postoperative period both before and after the onset of delirium.

Delirious patients had a complication rate of 86% (defined as more than 1 complication, since almost all patients had one complication in most cases being atrium fibrillation) compared to 32% among patients who did not develop delirium (table 1). Both groups differed significantly in the occurrence of systemic infection, re-operation and atrium fibrillation; non-compliance with medical treatment, behavioural problems and psychiatric consultation; and decubital ulcers and fall accidents, but not in delayed healing of the surgical wound and defibrillation and/or resuscitation (table 2).

Table 2

Postoperative complications for non-delirious (n=256) and delirious (n=40) patients*(n=296)

	Non-delirious	Delirious	All pts	Test-value	p-value
Delayed healing of surgical wound	9(4%)	2(18%)	11(4%)	Fisher's Exact	.65
Decubital ulcers	1(0%)	5(13%)	6(2%)	Fisher's Exact	<.001
Fall accidents	4(2%)	4(10%)	8(3%)	Fisher's Exact	.01
Non-compliance	0(0%)	2(5%)	2(1%)	Fisher's Exact	.02
Behavioural problems	4(2%)	10(25%)	14(5%)	Fisher's Exact	<.001
Psychiatric consultation	9(4%)	24(85%)	33(11%)	$X^2(1)=111.4$	<.001
Atrium fibrillation	151(59%)	34(85%)	185(63%)	$X^2(1)=9.99$	.002
Systemic infection	24(9%)	14(35%)	38(13%)	$X^2(1)=20.3$	<.001
Re-operation	28(11%)	12(30%)	40(14%)	$X^2(1)=10.76$	.001
Defibrillation/resuscitation	10(4%)	2(5%)	12(4%)	Fisher's Exact	.67
Other complications	67(26%)	21(53%)	88(30%)	$X^2(1)=11.48$	<.001

** These complications occurred both before and after the onset of delirium.*

Apart from postoperative state, being a possible etiological factor for delirium in all patients who developed postoperative delirium, multiple other factors were supposed to be possibly etiologically related to the occurrence of deli-

Table 3
Characteristics of delirium (n=40)

	Number of patients (%)	
Day of onset delirium:		
Day 1	19	48%
Day 2	9	23%
Day 3	6	15%
Day 4	2	5%
Unknown*	4	10%
Duration of delirium:		
1 or 2 days	9	23%
3-7 days	18	45%
8 or more days	9	23%
Unknown*	4	10%
Number of etiological factors per patient**:		
None	3	8%
1	4	10%
2	14	35%
3 or 4	13	33%
5 or 6	6	16%
Kind of etiological factors***:		
Intoxication	9	23%
Withdrawal	8	20%
Infection/Fever	15	38%
Metabolic disorder	29	73%
Anaemia	6	15%
Endocrinologic disorder	5	13%
Respiratory insufficiency	19	48%
Cardiovascular disorder	17	43%
Cerebrovascular disorder	3	8%

* *Unknown because of impossibility of sufficient assessment*

** *Possible etiological factors other than postoperative state*

*** *More than one etiological factor may have been rated*

rium in most patients (82%) (table 3). Metabolic disorders like electrolyte disturbances, uraemia, respiratory insufficiency (often requiring prolonged intubation) and cardiovascular disorders, such as decreased cardiac output, were among the most frequent supposed etiological factors for delirium.

Postoperatively, all patients received multiple medications both intravenously and orally. Since some medications like propofol, dopamine, midazolam etc. were generally given as a drip, it was not possible to calculate the exact dosage. Therefore, the medication used was expressed as the mean duration in days, during four days postoperatively. During the four days following surgery

delirious patients did not get significantly more medications compared to non-delirious patients, the mean number of medications being 17 and 16, respectively. In 23% (n=9) of the delirious patients intoxication, mainly with opiates, was judged to be (partly) responsible for the occurrence of delirium. It appeared that delirium was significantly associated with increased administration of propofol (p<.01), dobutamine (p=.03), dopamine (p<.01), midazolam (p<.01), morphine (p<.01), ranitidine (p<.01), and haloperidol (p<.01); and decreased use of flurazepam (p=.02), temazepam (p<.01), triamtereen (p<.01), naproxen (p<.01), paracetamol (p<.01) and acenocoumarol (p<.01). No significant differences between both groups were found in the use of nifedipine, corticosteroids, digoxine, furosemide, verapamil, nipride and theophylline to name the most important, with an anticholinergic effect associated, drugs [11].

Delirium was associated with a significant longer median length of stay, being 14 days for patients who developed delirium compared to 11 days for patients who did not (table 1). Patients who died during admission and patients who were discharged early within 6 days postoperatively to another hospital (for the normal postoperative after-care) were initially excluded because of the introduction of a bias. Including the early discharged patients, however, did not change the median length of stay for the non-delirious patients; and taking the patients who died into account increased the median length of stay for delirious patients with one day only, since both the mean and median length of stay for deaths was 69 days.

All four in-hospital deaths were patients with delirium. The mortality rate for delirious patients was significantly higher being 10% during admission and 7.5% after discharge compared with 0% and 0.4%, respectively, for non-delirious patients. The Odds Ratio for dying within 6 months of surgery, having gone through delirium, appeared to be high (OR=54, 95% CI=7-461).

Delirium also proved to be significantly related to discharge to a longterm care facility such as rehabilitative setting, nursing home, and other hospital or other department of own hospital for extended aftercare due to complications (table 1).

In table 3, next to the possible etiological factors for delirium described before, the main characteristics of delirium are presented. For most patients (48%),

Table 4
Characteristics of delirium: Treatment with haloperidol (n=25)

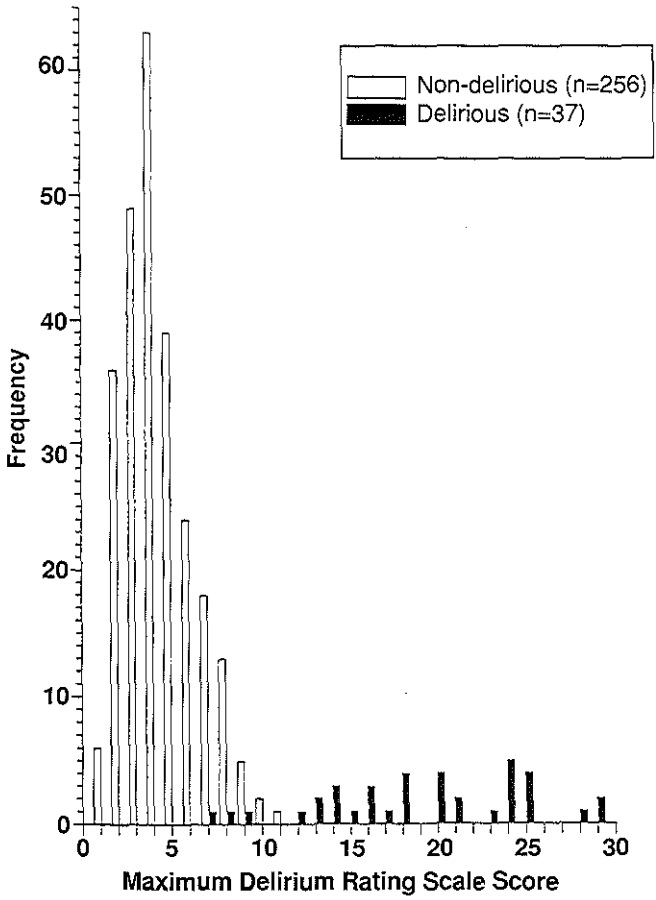
Treatment with haloperidol	Range	Median/mean
Day of onset (median)	1-11	3
Duration in days (median)	1-13	5
Maximum dosage in mg/day (SD) (mean)	2-25	9.6(6.8)

delirium started already on the first day postoperatively and never later than the fourth postoperative day. For four patients the day of onset and duration of delirium was unknown, since they were not formally assessable due to prolonged intubation or sedation (often because of agitation). They were judged to be delirious because they required physical restraint and sedation (propofol or midazolam) and/or haloperidol for treating supposed delirious symptoms like inappropriate behaviour (such as removing intravenous lines or other vital equipment), probable signs of hallucinations and/or suspicion, agitation with inverse day-night rhythm and severe cognitive deficits e.g. inability and/or unwillingness to co-operate. The median onset of delirium was on the first day postoperatively and the mean duration was five days with a range of 1-13 days (table 3).

Twenty-five (63%) of the delirious patients were treated with haloperidol for a median period of 5 days. The median onset of antipsychotic treatment was on

Figure 1

Frequency of maximum score on the Delirium Rating Scale for non-delirious (n=256) and delirious (n=37) patients



day 3 postoperatively and the mean maximum dosage ranged from 2-25 mg/day (table 4).

The frequency of the maximum scores on the DRS for delirious and non-delirious patients are shown in figure 1. The maximum score on the DRS, being an indication of severity of delirium, was significantly correlated with the maximum dosage of haloperidol the delirious patients received for treatment (r=.45, p=.027). Delirium, clinically judged to be mild (n=6), corresponded - not surprisingly since the scoring on the DRS is in fact also based on unstructured clinical assessments- to a lower maximum score on the DRS (mean maximum score=12, ranging from 7-16) than delirium judged to be of moderate or grave severity (n=25, mean maximum score=21.5, ranging from 14-29). Since clinical judgement added not much information, the maximum score on the DRS was used as a measure of severity of delirium. ß

In table 5 and table 6 the characteristics and profiles of the patients who died within a period of six months postoperatively are summarized. The mean age of the seven delirious patients who died did not differ significantly from that

Table 5
Characteristics of deaths (n=8)

Gender and mean age (SD) of all patients	3 women and 5 men, 71.4(6.8) years
Delirious	3 women and 4 men, 72.7(6.1) years
Non-delirious	male, 62 years
Kind of surgery*	5 CABG, 1 VR, 1 CABG+VR, 1 CABG+aneurysm LV
Presence of predictors	
Age ≥ 65 years	for 6 patients
Albumin ≤ 40 g/l	for 5 patients
Use of nifedipine	for 2 patients
PHE-ratio ≥ 13.35	for 2 patients
GHQ score > 7	for 3 patients
Mean (range) maximum haloperidol medication (mg/day); n=4	7(5-10)
Maximum DRS score, mean (range)**	17(1-25); 1 for non-delirious patient
Length of stay, mean (range)	39(9-120); 11 for non-delirious patient
Number of complications, mean (range)	3(0-5); 0 for non-delirious patient
Major complications	4 infections and 2 re-operations
Causes of death	Stroke; cardiac arrest; cardiac failure (n=4); unknown for patient without delirium

* *CABG=Coronary Artery Bypass Graft; VR=Valve Replacement; LV=Left Ventricle.*

** *n=6, since two patients were not assessable.*

of the delirious patients who survived this period. The one patient without delirium who died, was only 62 years old, did not have any predictors for deli-

Table 6
Clinical profiles of patients who died within 6 months postoperatively (n=8)

patient number	1	2	3	4	5	6	7	8
Delirium	yes	yes	yes	yes	yes	yes	yes	no
Gender	♂	♀	♀	♂	♂	♂	♀	♂
Age(years)	73	73	78	70	70	63	82	62
Kind of surgery	CABG	CABG+LV aneurysm	CABG+VR	CABG	VR	CABG	CABG	CABG
Presence of predictors								
-Age ≥ 65 yrs	yes	yes	yes	yes	yes	no	yes	no
-Albumin ≤ 40 g/l	yes	yes	yes	no	yes	no	yes	no
-PHE ratio ≥ 13.35	no	no	yes	no	yes	no	no	no
-GHQ > 7	no	yes	yes	no	yes	no	no	no
-Use of nifedipine	yes	no	no	yes	no	no	no	no
Number of complications	3	2	5	5	4	5	3	0
Maximum dosage haloperidol (mg/day)	0	0	7.5	5	5	0	10	0
Maximum DRS score	21	9	22	15	?	?	21	1
Length of stay	17	9	17	89	120	48	21	11

rium, experienced no complications postoperatively and had a normal length of hospital stay.

Delirium did not prove to be associated with less functional recovery, as measured on the DAL, at six months follow-up and also no significant difference was found in living situation at that time. Both delirious and non-delirious patients improved significantly ($p<.0001$ for both groups) in their functional status, as measured by their scores on the DAL at six months follow-up, indicating a better physical health with less limitations in daily activities than before surgery.

DISCUSSION

Consistent with previous studies among non-cardiac surgical patients [4,5,7-9], delirium was found to be strongly associated with the number and kind of postoperative complications, length of hospital stay and mortality rate. Since, to our knowledge, no data on course and outcome of delirium after cardiac surgery have been published to date, comparison with similar patients was not possible. Moreover, because in the different studies several definitions of 'a complication' are used, comparing the reported results with the findings of this study constitutes a problem. For example, in the study of Marcantonio et al. [7] only major complications such as cardiac arrest, renal failure requiring dialysis and stroke were rated, while in this study also other clinically relevant complications like behavioural problems and decubital ulcers were included, resulting in a complication rate of 86% in delirious patients compared with 32% in non-delirious patients.

Most of the complications occurring at about the same time as the onset of delirium were also rated as a possible etiological factor for delirium and headed under 'other complications' in comparing delirious and non-delirious patients. These were, next to atrium fibrillation and systemic infection, strongly related to the occurrence of delirium indicating that patients at risk for delirium were more seriously ill. On the other hand, the psychiatric and management problems and the decubital ulcers and fall accidents associated with delirium were rather the result than the cause of delirium, even more complicating recovery and prolonging length of stay.
The postoperative physical disorders judged to be etiologically related to the appearance of delirium corresponded to the etiological factors mentioned in the literature [1,2,5,10]. It remained, however, unclear what part the different disorders had in causing delirium. Forty-nine percent of the delirious patients had three or more possible etiological factors for delirium, especially metabolic disorders, respiratory insufficiency and cardiovascular disorders, once more underlining the multifactorial etiology of this syndrome. Although to date, most studies on delirium after cardiac surgery did not examine extensively all possible contributing etiological factors, especially not the postoperative ones, a relationship between delirium and the following postoperative disorders was reported: Dehydration, hyponatraemia and tracheostoma (meaning prolonged intubation) [12]; severity of postoperative illness and/or prolonged stay in the recovery room [13-15]; greater exposure to postoperative psychoactive and anticholinergic drugs [16,17]; and decreased cardiac output postoperatively [18]. Also, sleep deprivation is indicated as a possible provocative circumstance [12,15], but the distinction from sleep disturbance as a prodromal symptom of delirium is difficult to make.

Delirium was associated with both an increase and a decrease in the administration of a number of postoperative drugs, the kind of drugs used reflecting the severity of illness and the need for sedation, for instance in case of prolonged intubation. The increased use of morphine paralleled the decreased use of peripheral acting pain medication in delirious patients. The administration of propofol and midazolam, associated with delirium, may just have been to sedate patients already delirious. Also, treatment with the inotropics dopamine and dobutamine, related to delirium, is a sign of being haemodynamic less stable and thus more severely ill. To be able to estimate the, generally considered harmful, effects of anticholinergic drugs and benzodiazepines on cognitive functions, quantitative measurement of their plasma levels would have been necessary [8,11,16,17]. The only conclusion based on our findings may be that patients using medication found to be associated with delirium are probably receiving these because they are seriously ill, delirium being more associated with severity of illness than with the medications patients got.

The median length of stay for delirious patients was three (or four if deaths were included) days longer. The excess mean length of stay in the studies on delirium among non-cardiac surgical patients was reported to be 2, 10, and 8

days, respectively [4,5,7]. However, deaths were not excluded in these studies and, although length of stay, most probably, will not have been normally distributed, means and not medians were given. Moreover, other types of surgery were examined, the length of postoperative hospital stay also reflecting the complexity of the surgical procedure and the differences in necessary aftercare.

Delirium seems to be one of the best predictors for mortality both for in-hospital and post-discharge death, being 10% and almost 8%, respectively, for delirious patients, while none of the non-delirious patients died during admission and only one within 6 months postoperatively. Marcantonio et al. [7] reported a somewhat lower in-hospital mortality rate of 4% for non-cardiac surgical delirious patients compared with 0.3% for patients who did not develop delirium.

In delirium, death can be either the consequence of more severe physical illness, the tendency of delirium being proportional to the severity of illness, or the presence of delirium worsens the outcome independently of any physical cause of mortality, for instance by making management of the delirious patients and their physical illness more difficult [10]. Furthermore, it may also be possible that (agitated) delirium, by inducing an even more catabolic and stressful state with increased levels of stress-related hormones, further weakens the physical condition of the patient. In this study, the number of deaths was too small to draw any conclusions about a possible relationship between delirium and severity of illness on the one hand and death on the other hand. Six of the seven delirious patients, who died within 6 months were older than 65 years and five of them had a low level of albumin, both strong preoperative risk factors for postoperative delirium. This is in contrast with the only non-delirious patient who did not survive the follow-up period, being 62 years old and having no preoperative risk factors. Having survived the first 6 months following cardiac surgery, delirious and non-delirious patients showed a better functional status than before surgery and did not differ anymore in the presence of limitations in daily activities nor in their living situation, reflecting a better, comparable physical health for both groups at this point.

In many studies, especially of the group of Kornfeld [13,14,17,19], a diagnosis of postcardiotomy delirium was only made in case of a lucid interval of at least two days before the occurrence of delirium. However, similar to the results of Sadler [20], in this study in most patients no lucid interval was detected, delirium often starting on the first day postoperatively. The maximum scores on the DRS of the delirious patients slightly overlapped those of the non-delirious control patients, contrary to the findings of Trzepacz et al. [21], who did not find any overlap between delirious and normal, medically ill patients. Also, the ranges of the DRS scores were greater for both delirious and non-delirious patients than those reported by Trzepacz et al. [21]. A possible explanation may be our different, postoperative, patient sample and the fact that some patients were rated on the DRS, while already recovering from delirium, previously not being assessable due to intubation and/or sedation and

reduced consciousness. However, a reliable and valid case-finding instrument, also suitable for assessing patients who are not able to communicate (verbally) was missing at the time the study began. Since then, the Delirium Symptom Interview (DSI) is being developed considering, among others, the problem of assessment of non-communicative patients by adding an observational component to the instrument [22]. As the observational part of the DSI includes more or less the same signs as used in our study to diagnose uncommunicative patients, it is reasonable to assume that most delirious patients will have been detected, although not all correctly rated.

In conclusion, delirium after cardiac surgery is a multifactorial disorder, in which vulnerability factors like, for instance, advanced age and catabolic state (described in chapter 6), the extent of physiological stress -in this case cardiac surgery with CPB- patients are going through (see chapter 7) and (additional) intra- and postoperative physical disorders contribute to the occurrence of delirium. Delirium proved to be most strongly associated with severity of illness both pre- and postoperatively. Next to the serious illness, delirium itself possibly contributed to interference with uncomplicated recovery, thereby prolonging length of stay and increasing the risk of dying. Conscientious intra- and postoperative care and concern aimed at preventing major and minor complications may, in combination with an optimized preoperative physical condition of the patient undergoing cardiac surgery, decrease the occurrence of postoperative delirium and further improve clinical outcome after cardiac surgery.

REFERENCES

1. Lipowski ZJ. Delirium: Acute Confusional States. New York: Oxford University Press, 1990.
2. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990; 263: 1097-1101.
3. Thomas RI, Cameron DJ, Fahs MC. A prospective study of delirium and prolonged hospital stay. Arch Gen Psychiatry 1988; 45: 937-940.
4. Rogers MP, Liang MH, Daltroy LH. Delirium after elective orthopaedic surgery: risk factors and natural history. Int J Psychiatry Med 1989; 19: 109-121.
5. Levkoff SE, Safran C, Cleary PD, Gallop J, Phillips RS. Identification of factors associated with the diagnosis of delirium in elderly hospitalized patients. JAGS 1988; 36: 1099-1104.
6. Hemert AM van, Mast RC van der, Hengeveld MW, Vorstenbosch M. Excess mortality in general hospital patients with delirium. A 5-year follow-up of 519 patients seen in psychiatric consultation. J Psychosomatic Res 1994; 38: 153-154.
7. Marcantonio ER, Goldman L, Mangione CM et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994; 271: 134-139.
8. Gustafson Y, Berggren D, Brännström B, Bucht G, Norberg A, Hansson LI, Winblad B. Acute confusional states in elderly patients treated for femoral neck fracture. JAGS 1988; 36: 525-530.
9. Berggren D, Gustafson Y, Eriksson B, Bucht G, Hansson LI, Reiz S, Winblad B. Postoperative confusion after anaesthesia in elderly patients with femoral neck fractures. Anesth Analg 1987; 66: 497-504.
10. Lindesay J, Macdonald A, Starke I. Delirium in the elderly. Oxford, Oxford University Press, 1990.
11. Tune LE, Carr S, Hoag BS, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: Potential means for assessing risk of delirium. Am J Psychiatry 1992; 149: 1393-1394.

12. Egerton N, Kay JH: Psychological disturbance associated with open-heart surgery. Br J Psychiatry 1964; 110: 443-449.
13. Heller SS, Frank KH, Malm JR, Bowman FO, Harris PD, Charlton MC, Kornfeld DS: Psychiatric complications to open-heart surgery. N Engl J Med 1970; 283: 1015-1020.
14. Kornfeld DS, Heller SS, Frank KA, Edie RN, Barsa J: Delirium after coronary artery bypass surgery. J Thorac Cardiovasc Surg 1978; 76: 93-96.
15. Sveinsson IS: Postoperative psychosis after heart surgery. J Thorac Cardiovasc Surg 1975; 70: 717-725.
16. Summers WK: Psychiatric sequelae to cardiotomy. J Cardiovasc Surg 1979; 20: 471-475.
17. Tune LE, Damlouji NF, Holland A, Gardner TJ, Folstein MF, Coyle JT: Association of post-operative delirium with raised serum levels of anticholinergic drugs. Lancet 1981; 2: 651-653.
18. Heller SS, Kornfeld DS, Frank KA, et al: Postcardiotomy delirium and cardiac output. Am J Psychiatry 1979; 136: 337-339.
19. Kornfeld DS, Zimberg S, Malm JR: Psychiatric complications of open-heart surgery. N Engl J Med 1965; 273: 287-292.
20. Sadler PD: Nursing assessment of postcardiotomy delirium. Heart Lung 1979; 8: 745-750.
21. Trzepacz PT, Baker RW, Greenhouse J. A Symptom Rating Scale for Delirium. J Psychiat Res 1988; 23: 89-97.
22. Levkoff S, Liptzin B, Cleary P, Reilly CH, Evans D. Review of research instruments and techniques used to detect delirium. In: Miller NE, Lipowski ZJ (Eds.) Delirium. Advances in research and clinical practice. 1991; 3: 253-271.

Chapter 9

CONCLUDING REMARKS

Afterwards it is always easy to decide what should have been done, as was also the case in this study. Many problems and shortcomings only became clear during or even after the study. A very important issue appeared to be, not surprisingly, the DSM-III-R criteria used for diagnosing delirium. Although these are widely accepted, the fact that we did not operationalize them in a precise and strict way certainly diminished the generalizability of the results found in this study. Furthermore, it was a tremendous and expensive work to have all the patients being assessed by only two research psychiatrists, sometimes being assisted by a psychiatric resident. Structuring and standardizing the criteria used probably would have created the possibility for having the patients being evaluated by trained non-clinician interviewers, thereby increasing the reliability of the findings and decreasing the costs. Moreover, reliable replication of this study by other researchers would have been easier.
Although the use of the Symptom Rating Scale for Delirium (DRS) was to be preferred to other ways of detecting delirium, such as a clinical interview, cognitive screening instruments and psychomotor tests, one of the main drawbacks of this instrument was the reliance on unstructured clinical impressions for scoring of the different items. Again, this posed a problem regarding reliability and generalizability. Moreover, although there were only a few raters in this study, whose results of scoring of the DRS were regularly compared with each other and evaluated by the author of this thesis, the interrater reliability was not systematically ascertained.
Another problem, not thought of beforehand, proved to be the fact that many, especially seriously ill, patients being thus more susceptible for delirium were not able to communicate at the time the occurrence of delirium was seriously suspected. In those cases it was very difficult to decide on the onset, duration, phenomenology and severity of delirium.

Based on these experiences, we can very much agree with the guidelines formulated by Levkoff et al. [1]. According to them, a research instrument for the detection of delirium must 1) provide explicit operational definitions of the criteria used, 2) document individual symptoms of delirium and not only provide an overall diagnosis making it, for example, possible to relate clinical subtypes of delirium and certain etiologies, 3) contain criteria concerning onset and fluctuation, 4) be structured and standardized, 5) be short and easy to administer to seriously ill patients, and 6) include an observational part for assessing too sick, handicapped or non-communicative patients [1]. In future research on delirium it is advisable to take all this into consideration and, perhaps, to add serial pre- and postoperative EEG registration, a sensitive though not specific detection method, as one of the diagnostic tools [2].

It may be evident that in an optimal research, the circumstances and actions are standardized as much as possible. However, clinical reality is requiring continuous adaptations, especially in the case of many different departments working together. Although the groups of delirious and non-delirious patients statistically did not differ regarding various important aspects of medical his-

tory, anaesthesia, surgery and postoperative situation, they often had been treated differently. Therefore, in future research, much attention has to be paid to maximum standardization of the pre-, intra- and postoperative circumstances.

Of the five predictors found, age and the plasma level of albumin proved to be strongly predictive for the occurrence of delirium after cardiac surgery, indicating that elderly patients in a preoperatively catabolic state are more susceptible. A relationship between a low level of albumin and delirium had been established before in critically ill patients, but not in preoperative, rather 'healthy' patients. Also, the preoperative plasma aminoacid concentrations, generally, were low for both delirious and non-delirious patients showing a tendency to become even lower over time of surgery, apart from TRP and PHE. It is for the first time that the results from clinical research are supposing preoperative preventive measures. Restoration of a catabolic state e.g. the albumin level and suppletion with balanced aminoacid mixtures before operation, next to otherwise optimizing the physical condition of the patients undergoing cardiac surgery, may decrease the occurrence of postoperative delirium. Further controlled, clinical intervention studies are needed in order to confirm this hypothesis.

REFERENCES

1. Levkoff S, Liptzin B, Cleary P, Reilly CH, Evans D. Review of research instruments and techniques used to detect delirium. In: Delirium. Advances in research and clinical practice. Miller NE, Lipowski ZJ, Lebowitz BD (Eds) 1991; 3: 235-271.
2. Leuchter AF, Jacobson SA. Quantative measurement of brain electrical activity in delirium. In: Delirium. Advances in research and clinical practice. Miller NE, Lipowski ZJ, Lebowitz BD (Eds) 1991; 3: 231-247.

SUMMARY
Cardiac surgery has traditionally been associated with a particularly high rate of postoperative delirium. The reported incidence ranges from 2-57%, depending on the research design, the selection of patients, the type of cardiac surgery, the assessments methods and the criteria and definition of delirium. The current incidence of delirium after cardiac surgery is unknown and findings on predictive factors are inconsistent. Studies on the pathophysiology of delirium after surgery with cardiopulmonary bypass are largely lacking.
The clinical research presented in this thesis tries to elucidate the role of reduced cerebral tryptophan availability and of changes in plasma concentrations of the other large neutral aminoacids in the occurrence of delirium after cardiac surgery, in relation to the effects and degree of catabolism. Furthermore, the current incidence and predictive factors associated with delirium after cardiac surgery are examined. The clinical course and outcome of delirium are described.

Chapter 1.1 starts with a summary of the historical development of the concept of this disorder. It is remarkable that, despite the confusing variety of terms applied over the centuries to the same set of symptoms, the clinical description of delirium has been rather accurate and consistent. Originally, in the time of Hippocrates, phrenitis and lethargus, both associated with fever and characterized by cognitive, sleep and behavioural disturbances, were the terms used for the syndrome delirium. In fact, phrenitis represented the variant of delirium currently called the hyperalert-hyperactive type and lethargus the variant nowadays called the hypoalert-hypoactive type. Only in the late eighteenth century the term delirium came into use. By that time, it was recognized that delirium could occur both in a wide range of systemic diseases and as a postoperative complication. Bonhoeffer, in the beginning of the twentieth century, introduced "the exogenous reaction types", including delirium, as nonspecific acute mental disorders caused by disorders in the body outside the brain. Next, it became clear that also cerebral disorders as well as intoxication by drugs and poisons could give rise to the exogenous reaction types, thus delirium. Engel and Romano in the 1940's, who attempted to correlate clinical, psychological and encephalographic (EEG) data in patients with delirium, were the first researchers in the field of pathophysiology of delirium. They supposed that cerebral insufficiency due to decreased cerebral metabolism was the pathophysiological basis for delirium. Since then, following studies on (experimental) anticholinergic delirium, the role of a disturbed balance of cerebral neurotransmitters has been the focus of (research) attention.
In the second part of chapter 1 the diagnosis and symptomatology of delirium are described. Delirium is defined as a transient organic mental syndrome of acute onset, characterized by a global impairment of cognitive functions, a reduced level of consciousness, attentional abnormalities, increased or decreased psychomotor activity, and a disordered sleep-wake cycle. With the publication of the DSM-III in 1980, followed by the DSM-III-R in 1987, a standard descrip-

tion and explicit criteria for a diagnosis of delirium were provided. Comparison of the DSM-III-R criteria with the ICD-10 criteria, published in 1992, showed that the latter are more precise and strict. Therefore, they seem more specific, but less sensitive, and better to operationalize. In this chapter, the prodromal symptoms and clinical features of delirium are described in detail. The existence of different subtypes of delirium and the relation of phenomenology to etiology are discussed. Delirium is described to be associated with a higher mortality and morbidity rate, longer hospitalization and institutionalization.

Chapter 2 presents the results of a critical review of the literature on incidence of and possible risk factors for delirium after cardiac surgery. From the studies found, including a meta-analysis on the results of 44 studies by Smith and Dimsdale, the following problems became clear: First of all, delirium often was inadequately defined. Second, there appeared to be confusion about the time of onset of postcardiotomy delirium, some researchers requiring a lucid interval of 2-5 days, postoperatively, for a diagnosis of postcardiotomy delirium. Third, in some studies postoperative deaths were (partly) excluded. Fourth, the different selection of patients and the shift in type of cardiac surgery over time resulted in different patient samples with respect to, among others, gender- and age distribution, severity of illness, comorbidity and surgical procedures. Fifth, the sample sizes and, thus, the power of the surveyed studies were very different. Selecting only those studies in which delirium was adequately defined and more or less comparable to current criteria, yielded a total of 16 prospective and 3 retrospective studies. The incidences appeared to vary considerably, ranging from 3-47%, and the small overlap of the confidence intervals indicated the heterogeneity of the studies. This heterogeneity could not be explained by type of surgery, mean age or gender distribution. However, a significant relationship was found between year of publication and incidence of postcardiotomy delirium, the later publications showing a tendency towards a lower incidence. Since the assumption of homogeneity, necessary for meta-analysis, was not met, comparison of the results with respect to the effects of the possible risk factors age, gender and time on cardiopulmonary bypass, although reported frequently enough, was not possible.

In chapter 3 the literature on the possible pathophysiological mechanisms in the occurrence of delirium is reviewed. Hypotheses about the pathophysiology of delirium appeared to be speculative and largely based on animal research. Abnormalities of a number of neurotransmitters may be involved in different aspects (like arousal, alertness, attention and memory), clinical presentations (like hyper- or hypoalert, hyper- or hypoactive, with or without psychotic phenomena) and specific disorder-related forms of delirium (like anticholinergic delirium, hepatic encephalopathy, alcohol- and benzodiazepine withdrawal delirium and postoperative delirium). Deficits in the cholinergic system may underlie (some of the symptoms of) delirium. However, changes in the other neurotransmitters very probably also play an important role. An excess

of glutamate and dopamine is being held responsible for cellular damage and the psychotic features of delirium. And both an excess and a deficit of cerebral serotoninergic function have been associated with hepatic encephalopathy and postoperative delirium, respectively. Furthermore, overactivity of the noradrenergic system, possibly due to elevated levels of cerebral noradrenaline and supersensitivity of the alpha-adrenergic receptors may be related to specific forms of delirium, for example (alcohol) withdrawal delirium.
Moreover, all these neurotransmitter (=first messengers) alterations probably have an additive effect on dysfunction of the intracellular signal transducing system, i.c. the second and third messengers, by this influencing again neurotransmitter synthesis and release. Also, age-related changes in the brain may underlie the increased sensitivity of older patients to the development of delirium.

Then, in chapter 3.2 and 3.3, the relationship between cardiopulmonary bypass (CPB), a catabolic state and delirium on the one hand and abnormalities of thyroid function tests on the other hand is discussed. Physiological stressful events such as non-thyroidal diseases and catabolic conditions like systemic illness, starvation and accidental or surgical trauma predictably lead to alterations in the metabolism of the thyroid, giving rise to abnormal thyroid function tests. The so-called, resulting, low T_3 syndrome is generally viewed as a useful adjustment to illness in order to minimize the catabolic state and conserve energy. It is characterized by a decrease in the serum T_3 concentration, an increase in the rT_3 concentration, a normal or possibly lowered TSH concentration and a normal, increased or decreased T_4 concentration, depending on the severity of the stressful condition. As a consequence of cardiac surgery with CPB and hypothermia, concentrations of thyroid hormones also appeared to be changed. T_3 showed a striking decrease beginning with the induction of anaesthesia, decreased further during CPB and was normalized 1 week after surgery. The rT_3 first decreased during anaesthesia and CPB, only to start increasing shortly after surgery. One week after surgery the rT_3 had returned to normal values. Subsequently, the ratio rT_3:T_3 is expected to increase postoperatively. This may be considered as a measure for the extent of physiological stress, probably being prognostic in the outcome. It is important to stress that a low T_3 level may cause 1) a diminished transport of aminoacids and carbohydrates, possibly giving rise to substrate deficiency, thus inhibiting the synthesis of the directly substrate dependent neurotransmitters, especially acetylcholine and serotonin, and 2) a generally decreased metabolism through reduced synthesis of ATP. In this way, cerebral neurotransmission may also be influenced.

In chapter 3.4 the results of a preliminary study on the role of reduced plasma TRP in the occurrence of delirium are presented. Since TRP is the precursor of cerebral serotonin, a neurotransmitter involved in functions such as aggressive and impulsive behaviour, mood, motor activity and sleep that are disturbed during delirium, the amount of functional serotonin in the central nervous

system is dependent on -among other factors- its transport across the blood-brain barrier. It was hypothesized that a postoperative, thus catabolic, state may reduce TRP transport because of two important mechanisms: 1) the plasma concentration of the amino acids valine, isoleucine, leucine, tyrosine and phenylalanine, which compete with tryptophan for the transport-carrier at the blood-brain barrier, is increased due to degradation of muscle proteins; and 2) the plasma concentration of tryptophan is reduced because of induction of tryptophan pyrrolase. The results of this study showed a significantly lower mean plasma TRP concentration and plasma TRP ratio of the 7 delirious patients compared with postoperative and healthy controls suggesting a role for reduced TRP availability from plasma in postcardiotomy delirium.

Chapter 4 contains the description of the aims and methods of this study, that was conducted in the Thoraxcentre of the University Hospital Dijkzigt, which is a large (approximately 1000 beds), inner-city teaching hospital in Rotterdam, the Netherlands. The study took place from may 1991 through november 1992. During this period 331 patients undergoing various types of elective cardiac surgery were prospectively studied. Pre- and postoperative assessment including psychiatric and psychometric evaluation and laboratory investigations, the management of anaesthesia and cardiopulmonary bypass, and the research instruments are described and accounted for.

In chapter 5 the Symptom Rating Scale for Delirium (DRS) is evaluated. A diagnosis of delirium was based on mental status examination using the DSM-III-R criteria. The DRS was administered for measurement of (severity of) individual symptoms. The small overlap in the DRS scores of delirious and non-delirious patients indicated high discriminant validity. Furthermore, it was found that most delirious patients had no apparent delusions or hallucinations, that (almost) all showed psychomotor behaviour and sleep disturbances and that most of them had lability of mood and variability of delirious symptoms. The highest correlation found, existed between psychomotor behaviour and perceptual disturbances, which, in turn, correlated well with hallucination type and temporal onset of symptoms. The two dimensions and four clusters found both reflected, in our view, different degrees of severity of delirium, the patients with mainly psychotic features as demonstrated by factor 1 and cluster 3 (followed by cluster 2 and 1), showing more severe delirium and a higher DRS max. score than the patients with mainly cognitive and emotional disturbances as indicated by factor 2 and cluster 4. The supposed hierarchical character of the DRS was confirmed by Mokken Scale Analysis.

Chapter 6 presents the incidence and predictive factors found in this study. The incidence of delirium after cardiac surgery was 13.5% for the total study sample, 0% for the patients under the age of 60 years and 20% for patients of 60 years and older. Univariate analysis of the possible predictive factors showed that delirious patients were significantly older. Delirium was more common among patients included in the study as an inpatient, reflecting

severity of illness, and associated with poor physical functioning. Also, patients with cognitive dysfunction (MMSE score < 24) had higher rates of delirium. Furthermore, both the phenylalanine (PHE) ratio, the mean serum concentration of rT_3 and the ratio rT_3:T_3 discriminated delirious from non-delirious patients. Delirium was also related to a lower mean albumin concentration and a decreased vitamin B1 level. Nifedipine, a calcium re-uptake inhibitor for treatment of angina pectoris that has been associated with anticholinergic effects in vitro, was the only medication used preoperatively that was associated with delirium. The combination of predictors that resulted in the best discrimination between delirious and non-delirious patients consisted of age, the plasma level of albumin, the score on the General Health Questionnaire (GHQ), the value of the PHE ratio and the use of nifedipine, age and albumin concentration being the strongest predictive factors. These findings, apparently, did not support our hypothesis that a preoperative reduced TRP availability from plasma plays a role in the etiology of postcardiotomy delirium, since both TRP and TRP ratio were not different for delirious and non-delirious patients. However, the combination of the levels of aminoacids as included in the high PHE ratio (PHE:VAL+LEU+ILE+TYR+TRP) proved to be a predictor for delirium. Relative elevations of PHE as reflected in this ratio may block the uptake of TRP into the brain, all the more because of a particular affinity of the blood-brain barrier for PHE in preference of the other aminoacids and a low plasma TRP. It was concluded that a decreased TRP availability from plasma is a possible risk factor for delirium in the presence of a (relatively) increased PHE. Most probably, imbalances of the other aminoacids and cerebral neurotransmitters also play an important role in this cerebral derangement.

In chapter 7 the effects of cardiac surgery on cerebral TRP availability, plasma concentrations of the other neutral aminoacids, thyroid function tests and cortisol in relation to the occurrence of delirium are presented. Delirium was not explained by differences in intraoperative and anaesthesia variables. Contrary to our expectations, the mean plasma concentration of TRP increased and those of the other neutral aminoacids, except PHE, reduced over time, resulting in a rise of the ratios of TRP and PHE, postoperatively. This rise in the plasma concentrations of TRP and PHE may be due to decreased conversion of these aminoacids in their metabolites as a consequence of declined tetrahydrobiopterin synthesis and a diminished metabolic rate in the liver under hypothermia. Nevertheless, delirium appeared to be especially associated with a lower plasma level of TRP and a lower TRP ratio. The increase in TRP ratio over time proved to be significantly less for delirious patients. These results seem to support the hypothesis that a relationship between a reduced cerebral TRP availability from plasma and the occurrence of postoperative delirium may exist. This was sustained by the finding that in delirious patients, after the onset of delirium, the concentration of TRP (and the TRP ratio) declined again, contrary to the normalized concentrations of the other aminoacids and the further increased concentration of PHE. Delirium was also related to lower plasma levels of the methyl donors SER and MET, indicating an endangered

production of cerebral acetylcholine. The stressful nature of cardiac surgery became clear from the significant increase of the ratio rT_3:T_3, TSH and cortisol. However, delirious patients did not respond differently to surgery and did not prove to be more catabolic. In conclusion, an imbalance of cerebral neurotransmission constituting a decreased serotoninergic and cholinergic function on the one hand and a (relatively) increased activity of the dopaminergic (and noradrenergic) system may underlie the occurrence of delirium after cardiac surgery.

Chapter 8 describes clinical course and outcome of delirium. Delirium was found to be strongly associated with the number and kind of postoperative complications, length of hospital stay and mortality rate. In fact, delirium was an important predictor for both in-hospital and post-discharge mortality, being 10% and 8%, respectively for delirious patients, while none of the non-delirious patients died during admission and only one after discharge. Of the seven delirious patients who died within 6 months of surgery, six were older than 65 years and five had a preoperative low plasma level of albumin, both strong predictors for delirium. Delirious patients appeared to be more seriously ill and delirium was associated with psychiatric problems, fall accidents and decubital ulcers. Delirium appeared to be a multifactorial disorder, most patients having three or more possible etiological factors for delirium. Since quantative measurement of plasma levels of anticholinergic drugs and benzodiazepines were missing, the only conclusion based on our findings may be that patients using medication found to be associated with delirium were probably receiving these because they were seriously ill, delirium being more associated with severity of illness than with the medications patients got.

In chapter 9 some general considerations, regarding methodological and clinical implications of this study, are discussed and suggestions for further research are provided.

SAMENVATTING

Cardiochirurgische ingrepen worden vanouds in verband gebracht met een bijzonder hoog vóórkomen van een postoperatief delirium. De gerapporteerde incidentie varieert van 2-57%, afhankelijk van het onderzoeksontwerp, de selectie van patiënten, de soort ingreep, de detectiemethoden en de gebruikte criteria voor de diagnose delirium. De huidige incidentie van delirium na hartchirurgie is onbekend en de gegevens over voorspellende factoren zijn inconsistent. Studies over de pathofysiologie van het postoperatieve delirium ontbreken grotendeels.
Het klinische onderzoek dat in dit proefschrift wordt beschreven tracht de rol van een verminderde cerebrale beschikbaarheid van tryptofaan (TRP) en van veranderingen in de plasmaconcentraties van de andere grote, neutrale aminozuren bij het optreden van een delirium na een cardiochirurgische ingreep te verhelderen. Bovendien wordt gepoogd een relatie te leggen met de effecten en de ernst van een katabole toestand. Tevens wordt onderzocht wat de huidige incidentie en de risicofactoren zijn en wordt het klinische beloop en de uitkomst van delirium beschreven.

Hoofdstuk 1.1 begint met een samenvatting van de historische ontwikkeling van het concept van deze stoornis. Het is opvallend dat de klinische beschrijving van het delirium door de eeuwen heen tamelijk nauwkeurig en constant is geweest, ondanks de vaak verwarrende terminologie. Oorspronkelijk, in de tijd van Hippocrates, werden de termen phrenitis en lethargus gebruikt voor het delirante syndroom. Beide werden geassocieerd met koorts en gekenmerkt door cognitieve, slaap- en gedragsproblemen. Phrenitis wordt heden ten dage het hyperalerte-hyperactieve en lethargus het hypoalerte-hypoactieve delirium genoemd. Pas aan het eind van de achttiende eeuw kwam het begrip delirium in zwang. Inmiddels werd algemeen erkend dat delirium het gevolg kon zijn van vele verschillende systemische aandoeningen en van operatie. In het begin van deze eeuw introduceerde Bonhoeffer de "exogene reactietypen", waartoe ook het delirium werd gerekend, als niet specifieke, acute psychiatrische stoornissen ten gevolge van niet-cerebrale, lichamelijke ziekten. Al spoedig werd echter duidelijk dat deze exogene reactietypen ook veroorzaakt konden worden door cerebrale aandoeningen en door intoxicaties met medicijnen en vergiften. Engel en Romano, de eerste onderzoekers op het gebied van de pathofysiologie van het delirium, probeerden klinische, psychologische en EEG-gegevens van patiënten met een delirium met elkaar in verband te brengen. Zo kwamen zij tot de veronderstelling dat cerebrale insufficiëntie ten gevolge van een verminderd hersenmetabolisme de pathofysiologische basis voor het delirium vormt. In aansluiting aan onderzoeken naar het (experimentele) anticholinerge delirium, krijgt de mogelijke rol van een verstoorde neurotransmitterbalans veel aandacht.

In het tweede deel van hoofdstuk 1 worden de diagnostiek en de symptomatologie van het delirium beschreven. Delirium wordt gedefinieerd als een acute en voorbijgaande organisch-psychiatrische stoornis, gekenmerkt door een glo-

bale cognitieve achteruitgang, een gedaald bewustzijn, een verminderde aandacht, een toegenomen of afgenomen psychomotore activiteit en een gestoord slaap-waak ritme. De publicatie van de DSM-III in 1980, gevolgd door die van de DSM-III-R in 1987, voorzag in een standaardbeschrijving en in duidelijke criteria voor de diagnose delirium. De criteria van de ICD-10, die in 1992 uitkwam, bleken nauwkeuriger en strikter, waardoor deze waarschijnlijk specifieker, maar minder sensitief zijn en beter geoperationaliseerd kunnen worden. In dit hoofdstuk worden de prodromale verschijnselen en de klinische kenmerken van het delirium uitgebreid belicht. Het bestaan van verschillende varianten en het mogelijke verband tussen verschijningsvorm en etiologie worden behandeld. Tevens wordt ingegaan op de gerapporteerde relatie tussen delirium en hogere morbiditeit, mortaliteit, opnameduur en institutionalisering.

In hoofdstuk 2 worden de resultaten weergegeven van een kritisch literatuuronderzoek naar de incidentie van en mogelijke risicofactoren voor het delirium na hartchirurgie. Uit de gevonden studies en een meta-analyse door Smith en Dimsdale van 44 onderzoeken, komen de volgende problemen naar voren: Ten eerste was delirium vaak onvoldoende gedefinieerd. Ten tweede bleek er verwarring over het begin van een postcardiotomie delirium, omdat sommige onderzoekers deze diagnose alleen stellen als er sprake is van een postoperatief lucide interval van 2-5 dagen. Ten derde werden in sommige onderzoeken overledenen (gedeeltelijk) uitgesloten. Ten vierde resulteerde de verschillende selectie van patiënten en de verandering in soort chirurgische ingreep in de loop van de tijd in verschillende groepen patiënten met betrekking tot bijvoorbeeld leeftijds- en geslachtsverdeling, ernst van ziekte, (co)morbiditeit en chirurgische procedure. Ten vijfde waren de onderzoeksgroepen zeer wisselend van grootte en verschilde de kracht van de diverse studies daardoor aanzienlijk. Alleen de 16 prospectieve en 3 retrospectieve onderzoeken waarin delirium voldoende en min of meer vergelijkbaar met de huidige criteria was gedefinieerd, werden voor verdere beschouwing geselecteerd. De incidenties varieerden aanmerkelijk, van 3-47%, en de kleine overlap van de betrouwbaarheidsintervallen bevestigde de heterogeniteit van de studies. Deze heterogeniteit werd niet verklaard door de soort chirurgische ingreep noch door de gemiddelde leeftijd of de geslachtsverdeling. Er werd echter wel een statistisch significant verband gevonden tussen de incidentie van het delirium en het jaar van publicatie. De latere publicaties lieten in het algemeen lagere incidenties zien. Vergelijking van de resultaten met betrekking tot de effecten van mogelijke risicofactoren zoals leeftijd, geslacht, duur van perfusie en hypotensie door middel van een meta-analyse was door het ontbreken van homogeniteit niet mogelijk, hoewel hierover voldoende vaak verslag werd gedaan.

In hoofdstuk 3 wordt een literatuuroverzicht gegeven van mogelijke pathofysiologische mechanismen voor het optreden van een delirium. Hypothesen hierover blijken grotendeels speculatief en vooral gebaseerd op dierexperimen-

teel onderzoek. Stoornissen van verscheidene neurotransmittersystemen lijken betrokken te kunnen zijn bij verschillende aspecten van het delirium (zoals alertheid, aandacht, geheugen enz.), bij verschillende klinische verschijningsvormen (zoals hypo- of hyperalert, hypo- of hyperactief, met of zonder psychotische verschijnselen) en bij verschillende specifieke, met bepaalde aandoeningen verbonden, vormen van het delirium (zoals het anticholinerge en alcoholonttrekkingsdelirium, de hepatische encephalopathie en het postoperatieve delirium). Onderzoek heeft aangetoond dat tekorten in het cerebrale cholinerge systeem ten grondslag kunnen liggen aan het optreden van een delirium. Waarschijnlijk spelen hierbij veranderingen in de andere neurotransmitter systemen eveneens een belangrijke rol. Zo wordt een overmaat aan glutamaat en dopamine in de hersenen wel verantwoordelijk geacht voor cellulaire schade en voor de psychotische verschijnselen van het delirium. En zowel een overmatig als een verminderd functioneren van het cerebrale serotoninerge systeem is in verband gebracht met het optreden van respectievelijk een hepatische encephalopathie en een postoperatief delirium. Verder ligt overactiviteit van het noradrenerge systeem ten gevolge van een verhoogde noradrenalineconcentratie in de hersenen en supersensitiviteit van de alpha-adrenerge receptoren mogelijk ten grondslag aan bepaalde specifieke vormen zoals het alcoholonttrekkingsdelirum. Veranderingen in deze neurotransmitter (="first messengers")-concentraties hebben mogelijk een bijkomend effect op een dysfunctioneren van het intracellulaire signaal-geleidingssysteen, d.w.z. de "second and third messengers", waardoor vervolgens de aanmaak en afgifte van neurotransmitters weer beïnvloed wordt. Tevens kunnen met de leeftijd samenhangende veranderingen in de hersenen de oorzaak zijn van de toegenomen kwetsbaarheid voor een delirium.

Vervolgens wordt in hoofdstuk 3.2 en 3.3 het verband gelegd tussen cardiopulmonaire bypass (CPB), een katabole toestand en delirium aan de ene kant en afwijkingen in schildklierfunctietesten aan de andere kant. Fysiologisch stressvolle omstandigheden zoals niet-schildklier ziekten en katabole toestanden als systemische aandoeningen, verhongering en (chirurgisch) trauma blijken aanleiding te geven tot veranderingen in het schildkliermetabolisme. Deze stoornissen veroorzaken abnormale schildklierfunctietesten en worden wel het lage T_3 syndroom genoemd. Over het algemeen wordt het lage T_3 syndroom gezien als een nuttige aanpassing aan ziekte om zo katabolisme te beperken en energie te sparen. Het wordt gekenmerkt door een afname in de serum concentratie van T_3, een toename in de rT_3-concentratie, een normale of mogelijk afgenomen TSH-concentratie en een normale, toegenomen of afgenomen T_4-concentratie, afhankelijk van de ernst van de stressvolle omstandigheden. Als gevolg van hartchirurgie met CPB en hypothermie blijken eveneens veranderingen in het schildkliermetabolisme te ontstaan. T_3 blijkt gelijktijdig met de inductie van de anesthesie enorm afgenomen, tijdens CPB nog verder gedaald en na een week weer genormaliseerd. De rT_3 is tijdens anesthesie en CPB aanvankelijk gedaald om onmiddellijk na operatie in waarde te stijgen. Na een

week is de rT_3 weer normaal. De ratio rT_3:T_3 zal dientengevolge postoperatief in waarde toenemen. Deze mag beschouwd worden als een maat voor fysiologische stress, met mogelijk een prognostische betekenis voor het verdere ziektebeloop. Het is van belang dat een lage T_3-waarde 1) een verminderd transport van aminozuren en suikers tot gevolg heeft, wat aanleiding kan geven tot een substraat-tekort en op die manier de aanmaak van direct substraat-afhankelijke neurotransmitters, zoals acetylcholine en serotonine, kan verstoren; en 2) door een afgenomen ATP-aanmaak een algemeen verminderd metabolisme veroorzaakt. Op deze manier kan de neurotransmissie in de hersenen eveneens beïnvloed worden.

In hoofdstuk 3.4 wordt verslag gedaan van de resultaten van een voorstudie naar de rol van verminderd plasma tryptofaan (TRP) bij het optreden van een delirium. TRP is de precursor van cerebraal serotonine, een neurotransmitter betrokken bij functies als aggressief en impulsief gedrag, stemming, motore activiteit en slaap, die ook gestoord zijn bij het delirium. Nu is de hoeveelheid functioneel serotonine in het CZS afhankelijk van o.a. het transport van TRP over de bloed-hersenbarrière. De veronderstelling was dat een postoperatieve, katabole toestand op twee manieren aanleiding geeft tot een verminderd TRP-transport nl. 1) de plasmaconcentratie van de aminozuren valine (VAL), leucine (LEU), isoleucine (ILE), tyrosine (TYR) en phenylalanine (PHE), die met TRP wedijveren om het transporteiwit in de bloed-hersenbarriere stijgt ten gevolge van afbraak van spiereiwitten; en 2) de plasmaconcentratie van TRP daalt door inductie van het leverenzym TRP-pyrrolase. De resultaten van deze studie lieten een significant lagere, gemiddelde plasmaconcentratie van TRP en plasma TRP ratio zien voor delirante patiënten vergeleken met postoperatieve en gezonde controle personen. Dit leek de hypothese dat een verminderde TRP-beschikbaarheid uit plasma bij het delirium na hartchirurgie een rol speelt, te bevestigen.

In hoofdstuk 4 worden de doelen en methoden van deze studie beschreven. Deze werd uitgevoerd in het Thoraxcentrum van het Academische Ziekenhuis Rotterdam-Dijkzigt, een groot (bijna 1000 bedden tellend) opleidingsziekenhuis. De studie vond plaats vanaf mei 1991 tot en met november 1992. Gedurende deze periode werden 331 patiënten, die verschillende vormen van hartchirurgie ondergingen, prospectief bestudeerd. De pre- en postoperatieve psychometrische en psychiatrische onderzoeksmethoden en laboratoriumbepalingen, de anesthesie en CPB, en de gebruikte instrumenten worden uiteengezet en verantwoord.

In hoofdstuk 5 wordt de "Symptom Rating Scale for Delirium (DRS)" geëvalueerd. De diagnose delirium was baseerd op de DSM-III-R criteria en werd gesteld door middel van psychiatrisch onderzoek. De DRS werd afgenomen om (de ernst van) de individuele symptomen vast te stellen. De geringe overlap in DRS-scores van delirante en niet-deliriante patiënten toonde aan dat er sprake was van een hoge discriminerende validiteit. Verder werd gevonden dat de

meeste delirante patiënten geen duidelijke wanen of hallucinaties rapporteerden, dat (bijna) allen psychomotore stoornissen en slaapproblemen hadden en dat velen een labiele stemming en fluctuatie in de symptomatologie vertoonden. De hoogste correlatie van de DRS-items werd gevonden tussen psychomotore gedrag en stoornissen in de waarneming, wat weer gecorreleerd was met het type hallucinatie en begintijdstip van het delirium. De aangetroffen twee dimensies en vier clusters weerspiegelden, naar onze mening, een verschillende ernst van het delirium. De patiënten met psychotische kenmerken zoals naar voren komend in factor 1 en cluster 3 (gevolg door cluster 2 en 1) bleken ernstiger delirant en hadden een hogere DRS max. score dan de patiënten met vooral cognitieve en emotionele kenmerken zoals blijkend uit factor 2 en cluster 4. Het veronderstelde hiërarchische karakter van de DRS werd bevestigd door een Mokken Schaal Analyse.

Hoofdstuk 6 geeft de resultaten weer van het onderzoek naar incidentie van en predictieve factoren voor het delirium na hartchirurgie. De gevonden incidentie is 13.5% voor de gehele studiesteekproef, 0% voor de patiënten onder de 60 jaar en 20% voor de patiënten ouder dan 60 jaar. Univariate analyse van mogelijk voorspellende factoren liet zien dat delirante patiënten significant ouder waren. Verder bleek delirium meer voor te komen bij patiënten die klinisch in het onderzoek waren ingesloten, wat een afspiegeling van ernst van ziekte is, en geassocieerd met slechter lichamelijk functioneren. Patienten met aanwijzingen voor verminderd cognitief functioneren (MMSE < 24) werden eveneens vaker delirant. Ook bleken de phenylalanine (PHE) ratio, de gemiddelde serumconcentratie van T_3 en de ratio rT_3:T_3 delirante van niet-delirante patiënten te onderscheiden. Delirium bleek eveneens gerelateerd aan een lage plasma-albumineconcentratie en een verlaagde vitamine B-1 spiegel. Nifidipine, een calcium heropname-remmer voor de behandeling van angina pectoris met anticholinerge eigenschappen in vitro, was de enige preoperatieve medicatie verband houdend met delirium. De combinatie van de vijf predictoren leeftijd, de plasmaconcentratie van albumine, de score op de Algemene Gezondheidsvragenlijst (AGV-30), de waarde van de PHE-ratio en het gebruik van nifidipine bleek het beste delirante van niet-delirante patiënten te onderscheiden. Leeftijd en albumine waren de sterkste voorspellers.

Deze bevinding leek onze hypothese dat een verminderde preoperatieve TRP-beschikbaarheid uit plasma een rol speelt in de etiologie van het delirium niet te bevestigen. Immers, noch de TRP noch de TRP-ratio waren voor delirante en niet-delirante patiënten verschillend. De combinatie van de concentraties van aminozuren zoals weergegeven in de hoge PHE-ratio (PHE:VAL+LEU+ILE+TYR+TRP) bleek echter wel een predictor voor delirium. De opname van TRP in de hersenen zou door deze relatieve toename van PHE ten opzichte van de andere aminozuren belemmerd kunnen worden, te meer omdat de concentratie van plasma TRP zeer laag was en PHE een hogere affiniteit voor de bloed-hersenbarrière heeft dan de andere aminozuren. Hieruit kan men concluderen dat in aanwezigheid van een (relatieve) stijging van PHE, een verminderde be-

schikbaarheid van TRP uit plasma een mogelijke risicofactor voor het delirium vormt. Andere aminozuren en neurotransmittors spelen hoogstwaarschijnlijk ook een rol bij deze ontregeling in de hersenen.

In hoofdstuk 7 worden de resultaten weergegeven van de effecten van hartchirurgie op de cerebrale TRP-beschikbaarheid, op de plasmaconcentraties van de andere aminozuren, op de schildklierfunctietesten en op cortisol, in relatie tot het optreden van een delirium. Delirium kon niet verklaard worden door verschillen in intraoperatieve variabelen of anesthesie. Tegen de verwachting in bleek de gemiddelde TRP-concentratie postoperatief gestegen en die van andere aminozuren, behalve van PHE, gedaald. Dit had een stijging van de TRP-ratio en PHE-ratio tot gevolg. Deze toename van TRP en PHE was mogelijk het gevolg van een verminderde omzetting van de beide aminozuren door een afgenomen aanmaak van tetrahydrobiopterin en verlaagde metabole omzetting in de lever door de hypothermie. Niettemin bleek delirium met name verband te houden met een lagere plasmaconcentratie van TRP en een lagere TRP-ratio. Ook bleek de toename in TRP-ratio significant geringer voor delirante patiënten. Deze bevindingen lijken de veronderstelling dat een verminderde cerebrale TRP beschikbaarheid een rol speelt bij het optreden van een delirium te ondersteunen. Dit werd verder gestaafd door het feit dat na het begin van het delirium de TRP-plasmaconcentratie en de TRP-ratio wederom gedaald bleken. Dit in tegenstelling tot de andere aminozuren, die genormaliseerd waren of, zoals PHE, verder gestegen. Delirium werd bovendien in verband gebracht met lagere plasma concentraties van de methyldonoren serine (SER) en methione (MET), wat een aanwijzing was voor een bedreigde productie van cerebraal acetylcholine. Hartchirurgie bleek een lichamelijk stressvolle gebeurtenis, gezien de significante toename van de ratio rT_3:T_3, TSH en cortisol. In dit onderzoek kon echter niet worden aangetoond dat delirante patiënten op een andere manier reageerden op operatie of meer katabool waren. Samenvattend kan op basis van de uitkomsten van dit onderzoek geconcludeerd worden, dat een verstoorde cerebrale neurotransmissie mogelijk ten grondslag ligt aan het optreden van een delirium na hartchirurgie. Hoogst waarschijnlijk speelt enerzijds een verminderd serotoninerg en cholinerg functioneren en anderzijds een (relatief) toegenomen activiteit van het dopaminerge en (noradrenerge) systeem hierbij een rol.

In hoofdstuk 8 worden het klinisch beloop en de uitkomst van het postoperatieve delirium beschreven. Er bleek een sterke relatie tussen het optreden van een delirium enerzijds en postoperatieve complicaties, opnameduur en sterfte anderzijds. Delirium was een belangrijke voorspeller voor sterfte. Tijdens opname overleed 10% van de patiënten met een delirium en niemand van de niet-deliranten; binnen 6 maanden na ontslag uit het ziekenhuis bleek nog eens 8% van de delirante patiënten gestorven in vergelijking met één patiënt die geen delirium had doorgemaakt. Van de, binnen 6 maanden na operatie, overleden delirante patiënten waren er zes ouder dan 65 jaar en hadden er vijf een preoperatief lage albumine-concentratie, beide sterke voorspellers voor

een delirium. Delirante patiënten waren lichamelijk zieker en hadden meer psychiatrische problemen, valaccidenten en decubitiswonden. Ook uit deze studie kwam naar voren dat delirium een multifactoriële aandoening is. Meestal waren er drie of meer mogelijke oorzaken voor het delirium aanwijsbaar. Aangezien anticholinergica en benzodiazepinen niet quantitatief bepaald waren, kon geen uitspraak gedaan worden over de relatie met delirium. Er kon slechts geconcludeerd worden dat het optreden van een delirium waarschijnlijk meer verband houdt met de ernst van de ziekte dan met de gebruikte medicatie.

In hoofdstuk 9 worden enige methodologische en klinische aspecten van de studie besproken en worden enkele suggesties voor verder onderzoek gedaan.

DANKWOORD

Aan de in dit proefschrift beschreven studie hebben meegewerkt de afdelingen psychiatrie (hoofd: Joost Schudel), Thoraxchirurgie (hoofd: Egbert Bos), Thoraxanesthesiologie (hoofd destijds: Omar Prakash, wnd. hoofd: Ronald Schepp), Cardiologie (hoofd: J.R.T.C. Roelandt), Nucleaire Geneeskunde (hoofd: Erik Krenning), de Centrale Dienst Automatisering Informatieverwerking (Bert van Ooijen, hoofd informatiecentrum) en het Centraal Klinisch Chemisch Laboratorium (hoofd: Jan Lindemans) van het Academisch Ziekenhuis Rotterdam Dijkzigt en het Centrum voor Klinische Besliskunde (hoofd: Dik Habbema; Instituut Maatschappelijke Gezondheidszorg) en de werkgroep Pathofysiologie van Gedrag (hoofd: Lolke Pepplinkuizen) van de Erasmus Universiteit Rotterdam. Graag wil ik al diegenen die een bijdrage geleverd hebben aan deze studie en de patiënten die hun medewerking aan het onderzoek hebben verleend, van harte bedanken. Zonder hen allen was dit proefschrift niet tot stand gekomen.

Ik ben mijn promotoren Lolke Pepplinkhuizen en Joost Schudel bijzonder erkentelijk voor het feit dat zij mij in de gelegenheid hebben gesteld het onderzoek uit te voeren en tot een goed einde te brengen en ik dank hen voor hun bijdrage. Peter Moleman (afdeling Psychiatrie AZR-Dijkzigt; Moleman Research BV) heeft, met name bij de eerste verkennende stappen op weg naar dit onderzoek, een belangrijke ondersteunende rol gespeeld. Ook Bert van Hemert en Michiel Hengeveld zijn bij het vervaardigen van het protocol, de uitvoering van het onderzoek en het schrijven van dit proefschrift een belangrijke hulpbron en toetssteen voor mij geweest. Erik Krenning heeft het mogelijk gemaakt dat de schildklierfunctiemetingen verricht konden worden en hem en zijn afdeling ben ik bijzonder erkentelijk voor de constructieve en leerzame discussies.

Dit onderzoek was niet mogelijk geweest als niet anderen klinische werkzaamheden van mij hadden overgenomen. Ik ben AnneMarie van Hulst zeer dankbaar voor de loyale wijze waarop zij gedurende langere tijd de Psychiatrische Consultatieve Dienst heeft waargenomen. Walter van den Broek heeft een belangrijke bijdrage aan dit onderzoek geleverd. Hij heeft mij bijgestaan bij zowel het opzetten als de uitvoering van de studie en, in een later stadium, de Psychiatrische Consultatieve Dienst ondersteund.

Vele student-assistenten en arts-assistenten zijn, direct of indirect, op een waardevolle en onontbeerlijke wijze bij het onderzoek betrokken geweest. Ik ben Cora Aaldijk, Pety de Bruin, Marco Jansen, Isis Koolhoven, Ellen Kruidenier, Michel Kruyk, Joke van Marion, Tom van Mierlo, Michiel Morshuis, Jacqueline Smorenburg, Mabel Stolk, Monique Tjon-A-Tsien, Jolien Tuyl, Sytze van der Veen, Monica Vincent, Marielle Vorstenbosch, Monique Wendel en Ingeborg Zandijk hiervoor bijzonder erkentelijk.

De uitvoering van de studie vond plaats in het Thoraxcentrum. Egbert Bos wil

ik danken voor de gelegenheid door hem geboden en de daadwerkelijke ondersteuning door hem verleend. Zowel de poliklinische als de klinische medewerkers van het Thoraxcentrum hebben door hun behulpzame en gastvrije houding steun geboden bij de uitvoering van het onderzoek. Met name Mijndert Taams wil ik danken voor zijn collegiale en enthousiaste ondersteuning bij de opstart van het onderzoek en Annette van de Schelde voor haar grote bereidwilligheid om op al onze vragen keer op keer weer een antwoord te vinden. De medewerkers van de afdeling Thoraxanesthesiologie ben ik zeer erkentelijk voor hun behulpzaamheid bij de uitvoering van de studie. Marianne Wijers-Hille beschreef voor mij de techniek van de extra corporale perfusie.

Bert van Ooyen wil ik danken voor zijn voortdurende ondersteuning bij het beheer van de data.
Het Centrum voor Klinische Besliskunde heeft een belangrijke rol gehad bij het vervaardigen van het onderzoeksprotocol en de analyse van de gegevens. Het laatste jaar van de studie, dat vooral gewijd was aan het analyseren en beschrijven van de resultaten, heb ik hier een warm, gastvrij en leerzaam onderkomen mogen vinden. Ik wil Dik Habbema bijzonder danken voor de door hem geboden mogelijkheden en zijn constructief kritische commentaar. Ik wil met name Frits Roest vermelden die mij in deze fase aan de hand genomen heeft en mij, op geduldige wijze, de beginselen van het analyseren van gegevens heeft duidelijk gemaakt. Beste Frits, de tijd die jij in dit proefschrift hebt gestoken en de begeleiding die ik van je gekregen heb, zijn voor mij heel waardevol geweest en ik wil je hiervoor van harte danken.

De medewerkers van de verschillende laboratoria die de bepalingen van de biochemische variabelen hebben uitgevoerd ben ik hiervoor zeer erkentelijk. Durk Fekkes (Werkgroep Pathofysiologie van Gedrag) verrichtte de metingen van de aminozuren in plasma en leverde een belangrijke bijdrage aan de interpretatie en beschrijving van de resultaten ervan. Hans van Toor (laboratorium Inwendige Geneeskune III, schilklieronderzoek) was verantwoordelijk voor de metingen van de schildklierfuncties en het plasma cortisol. Het CKCL (hoofd: Jan Lindemans) was bereid zorg te dragen voor de bepalingen van de (pre)albumine, B-vitamines en foliumzuur-spiegels.

Marga Bosbaan heeft er als een cerberus voor gewaakt dat tijdens het schrijven van het proefschrift alleen de hoognodige informatie van buitenaf tot mij doordrong. Tiny Zaanen was altijd weer bereid allerlei klussen, vaak op het laatste moment, voor mij op te knappen en mij administratief te ondersteunen. Jullie beiden dank ik voor alle steun die ik, al die jaren, van jullie heb mogen krijgen.

Vele mensen die niet betrokken zijn geweest bij de vervaardiging van dit proefschrift waren desalniettemin, indirect, bijzonder belangrijk voor de totstandkoming ervan. Mijn collega's ben ik zeer erkentelijk voor hun stimule-

rende steun. Mijn ouders en mijn stiefvader dank ik voor de vanzelfsprekendheid waarmee zij mij, van jongs af aan, gesteund hebben in mijn school- en studiekeuzen. Ik hoop dat ook mijn broers en zussen trots op me kunnen zijn. Jannie en Miel ben ik dankbaar voor hun wijze beschikbaarheid. Mijn vrienden en vriendinnen dank ik voor hun bemoedigende, inspirerende en warme vriendschap.

Tot slot, Walter, jij maakt dat mijn leven vol kleur is.

CURRICULUM VITAE

De schrijfster van dit proefschrift werd op 9 november 1952 te Medan (Indonesië) geboren. Zij doorliep het Mollerlyceum te Bergen op Zoom, waar zij in 1971 het diploma gymnasium-ß behaalde. In datzelfde jaar begon zij haar studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. Op 17 februari 1978 werd zij tot arts bevorderd. Tijdens haar studie Geneeskunde deed zij in 1974 gedurende een half jaar een onderzoekstage aan het "Institut de Cancérologie et d'Immunogénétique" te Parijs. Zij begon haar specialisatie psychiatrie (opleider Prof.Dr. G.A. Ladee) in 1978 met het keuzejaar psychotherapie in het Psychotherapeutisch Centrum "de Viersprong" te Halsteren (opleider Prof.Dr. P.J. Jongerius), in 1979 gevolgd door de basisopleiding psychiatrie in het Academisch Ziekenhuis Dijkzigt te Rotterdam. In het kader van de opleiding tot psychiater volgde zij een drie maanden durende stage Inwendige Geneeskunde in het Dijkzigt ziekenhuis (Prof.Dr. J. Gerbrandy), waarna zij tot augustus 1983 gedurende anderhalf jaar als arts-assistent werkzaam was op de afdeling neurologie (opleider Prof.Dr. A. Staal) van hetzelfde ziekenhuis. Op 1 februari 1983 werd zij ingeschreven in het specialistenregister, waarna zij op 1 augustus 1983 als staflid haar werkzaamheden op de afdeling Psychiatrie van het Academisch Ziekenhuis Rotterdam-Dijkzigt begon. In 1984 bracht zij enkele maanden door in "The Montefiori Medical Center" (F.P. McKegney, "Albert Einstein College of Medicine") en "The Mount Sinai Hospital" (Prof. J.J. Strain) te New York om kennis op te doen op het gebied van de consultatieve en liaison-psychiatrie. Zij bekleedt thans de functie van hoofd van de Medisch Psychologische en Psychiatrische Consultatieve Dienst. Zij is tevens psychoanalytisch psychotherapeut en supervisor van de Nederlandse Vereniging voor Psychoanalytische Psychotherapie.

PUBLICATIES

1. Mast RC vd. De psychiater en de behandeling van pijn. IKR-bulletin Pijn en kanker 1985; 4: 15-17.
2. Mast RC vd, Hengeveld MW. Wat te doen en wat te laten; een patiënte met veel lichamelijke klachten. Ned Tijdschr Geneesk 1987; 131: 1153-1155.
3. Mast RC vd. Psychologische reacties en psychiatrische stoornissen ten gevolge van hersenmetastasen. Medische en verpleegkundige zorg voor patiënten met hersenmetastasen. "Omgaan met stress en spanning". St. Opleidingen Gezondheidszorg Midden-Brabant. 1987; 19-25.
4. Mast RC vd, Moleman P. Het delirium in het algemene ziekenhuis. Reactie op commentaar betreffende medicamenteuze behandeling van het delirium. Ned Tijdschr Geneesk 1988; 132: 1128-1129.
5. Mast RC vd, Moleman P. Het delirium in het algemene ziekenhuis. Ned Tijdschr Geneesk 1988; 132: 617-620.
6. Mast RC vd. Sexual abuse by their helping professionals: Women at risk. Nordisk Sexologi 1988; 6: 222-227.
7. Hengeveld MW, Huyse FJ, Mast RC vd, Tuinstra CL. A proposal for standardization of Psychiatric Consultation-Liaison data. Gen Hosp Psychiat 1988; 10: 410-422.
8. Metz ME, Schudel WJ, Mast RC vd. Suïcide à deux. Maandbl Geest Volksgezondh 1988; 43: 154-167.
9. Kooiman CG, Wetering BJM vd, Mast RC vd. Spoedeisende hulp in een algemeen ziekenhuis. Med Contact 1988; 43: 11-14.
10. Mulder LJMM, Mast RC vd, Meerwaldt JD. Generalised chorea due to digoxin toxicity. Brit Med J 1988; 296: 1262.
11. Mast RC vd, Hengeveld MW, Bannink M. Depressies bij somatisch zieke patienten. Ned Tijdschr Geneesk 1989; 133: 713-716.
12. Mast RC vd, Hengeveld MW, Bannink M. Depressies bij somatisch zieke patienten (2 reacties op commentaar). Ned Tijdschr Geneesk 1989; 133: 1332-1333.
13. Mast RC vd, Huyse FJ. Ernstige en bedreigende lichamelijke ziekten en traumata: het vóórkomen van de posttraumatische stress-stoornis miskend ? Tijdschr Psychiat 1989; 31(3).
14. Mast RC vd, Erdman RAM. Begeleiding van hartpatiënten. Medifo: Liaison-psychiatrie 1989; 5: 10-13.
15. Hengeveld MW, Huyse FJ, Mast RC vd. Consultatieve psychiatrie in Nederland: de stand van zaken. Maandbl Geest Volksgezondh 1989; I: 31-46.
16. Kooiman CG, Wetering BJM vd, Mast RC vd. Clinical and demographic characteristics of emergency department patients in the Netherlands: self-versus physician-referred patients. Am J Emergency Med 1989; 7: 632-637.
17. Mast RC vd. Psychofarmaca en de behandeling van pijn. IKR Bull 1990; 14: 31-32.
18. Bonsel GJ, Erdman RAM, Mast RC vd, Balk AHMM, Maas PJ vd. Psychosociale aspecten van harttransplantatie; 4 jaar ervaring. Ned Tijdschr Geneesk 1990; 134: 227-231.
19. Mast RC vd. Diagnostiek en behandeling van de patiënt met een delier. TGO/JDR 1991; 16: 20-25.
20. Mast RC vd, Fekkes D, Moleman P, Pepplinkhuizen L. Is postoperative delirium related to reduced plasmatryptophan ? Lancet 1991; 338: 851-852.
21. Mast RC vd, Broek WW vd, Moleman P. Een psychiatrische stoornis op een intensive care-afdeling. Ingezonden brief n.a.v. betreffende artikel. Ned Tijdschr Geneesk 1991; 135: 1460.
22. Hengeveld MW, Mast RC vd, Tuinstra CL. Management of patient-staff and intra-staff problems in psychiatric consultations. Gen Hosp Psychiat 1991; 13: 31-38.
23. Lely AJ vd, Foeken K, Mast RC vd, Lamberts SWJ. Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist Mifepristone (RU 486). Ann Int Med 1991; 114: 143-144.
24. Gool AR v, Mast RC vd, Moleman P. Orofaciale dyskinesie: een bijwerking van antidepressiva ? Acta Neuropsychiat 1991; 3: 1-4.
25. Gerritsen EJ, Mast RC van der. Psychogene afonie: een goed te behandelen conversie. Ingezonden brief n.a.v. desbetreffende artikel. Ned Tijdschr Geneesk 1992; 136: 1320-1321.
26. Derksen JJL en Mast RC van der (eds). Psychoanalytische psychotherapie en persoonlijkheidsstoornissen. Academische Uitgeverij Amersfoort, 1993.
27. Derksen JJL, Mast RC van der. Psychoanalytische behandeling en karakter. In: Psychoanalytische psychotherapie en persoonlijkheidsstoornissen. Derksen JJL en Mast RC van der (eds). Academische Uitgeverij Amersfoort, 1993.
28. Huyse FJ, Verwey B, Op den Velde W, Mast RC van der. Ziekenhuispsychiatrie: Naar een

integratie van de consultatieve psychiatrie en de afdeling psychiatrie van het algemeen ziekenhuis. Tijdschr Psychiat 1993; 35: 132-142.
29. Aaldijk C, Broek WW van den, Mast RC van der. De mogelijke rol van tryptofaan bij hepatische encephalopathie. Acta Neuro Psychiatrica 1993; 4: 71-75.
30. Smorenburg JMJ, Mast RC van der, Jonghe F de. Psychodynamische persoonlijkheidsdiagnostiek. Tijdschr Psychiat 1994; 36: 155-168.
31. Mast RC van der, Smorenburg JMJ, Jonghe F de. Psychoanalytische steungevende psychotherapie. Tijdschr Psychiat 1994; 36: 254-265.
32. Mast RC van der. Editorial. Tijdschr Psychiat 1994; 36: 153-154.
33. Hemert AM van, Mast RC van der, Hengeveld MW, Vorstenbosch M. Excess mortality in general hospital patients with delirium. A 5-year follow-up of 519 patients seen in psychiatric concultation. J Psychosomatic Res 1994; 38: 339-346.
34. Janssen HLA, Brouwer JT, Mast RC van der, Schalm SW. Suicide associated with alpha-interferon therapy for chronic viral hepatitis. J Hepatology 1994: Accepted for publication.
35. Smals GLM, Mast RC van der, Speckens AEM. Alcohol abuse among general hospital in-patients according to the Munchner Alcoholism Test (MALT). Gen Hosp Psychiatry 1994; 16: 125-130.
36. Sybrandy C, Mast RC van der. Trichotillomanie. Modern Medicine 1994: Accepted for publication.
36. Naarding P, Mast RC van der. (Pathological) crying: A psychiatric symptom? In preparation.
37. Mast RC van der, Roest FHJ. Delirium after cardiac surgery: A critical review. Submitted for publication.
38. Mast RC van der, Broek WW van den, Fekkes D, Pepplinkhuizen L, Roest FHJ. Delirium following cardiac surgery: Incidence and predictive factors. Submitted for publication.
39. Mast RC van der, Fekkes D, Broek WW van den, Pepplinkhuizen L, Roest FHJ. Delirium after cardiac surgery: The role of reduced cerebral tryptophan availability, changes in plasma concentrations of the other amino acids and the influence of a catabolic state. In preparation.
39. Mast RC van der, Krenning EP, Broek WW van den, Roest FHJ. Delirium, catabolic state, cardiopulmonary bypass (CPB) and thyroid function: The low T3 syndrome. In preparation.
40. Mast RC van der, Broek WW van den, Roest FHJ. The Symptom Rating Scale for delirium as an instrument to detect and measure the severity of delirium in a surgical population. In preparation.
41. Mast RC van der. Pathophysiology of delirium: The possible role of aminoacids and neurotransmitters: A review. In preparation.
42. Mast RC van der, Broek WW van den, Roest FHJ. Clinical course and outcome of delirium after cardiac surgery. In preparation.
43. Mulder CI, Antoni MH, Mast RC van der, Duivenvoorden HJ. Determinants of psychiatric symptoms during one year in HIV-infected homosexual men. Submitted for publication.
44. Verkes RJ, Mast RC van der, Kerkhof AJFM, Fekkes D, Hengeveld MW, Tuyl JP, Kempen GMJ. Platelet 5-HT, MAO activity and 3H-Paroxitine binding related to impulsive suicide attempts and borderline personality in recurrent behaviour. Submitted for publication.