Netherlands
The Journal of Medicine
PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

MISSION STATEMENT

The mission of the journal is to serve the need of the internist to practice up-to-date medicine and to keep track with important issues in health care. With this purpose we publish editorials, original articles, reviews, controversies, consensus reports, papers on speciality training and medical education, book reviews and correspondence.

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Cover
Mezzotint 'untitled' by Caroline Koenders,
for details see page 25.

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An annual subscription to The Netherlands Journal of Medicine (ISSN 0300-2977) consists of 11 issues. Issues within Europe are sent by standard mail and outside Europe by air delivery. Resigning from your subscription is possible in writing, two months before the year ends.

Subscription fee
The annual subscription fee within Europe is € 650,00, for the USA € 665,00 and for the rest of the world € 675,00. Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis.

Payment method
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CITED IN: BIOSIS DATABASE; ELSEVIER BIOBASE/CURRENT AWARENESS IN BIOLOGICAL SCIENCES, CURRENT CONTENTS (CLINICAL MEDICINE); EMBASE/EXCERPTA MEDICA; INDEX MEDICUS (MEDLINE)

Jos van der Meer

Theo Thien

Anton Stalenhoef

Paul Smits

Geeralien Derksen-Willemsen

This is the first issue of the renewed Netherlands Journal of Medicine.
When Professor Hoepelman asked me last year whether 'Nijmegen' would be willing to serve as the new editorial board for The Netherlands Journal of Medicine, it did not take me long to agree. I immediately asked my close colleagues Professor Theo Thien, Professor Anton Stalenhoef and Professor Paul Smits to join me in this venture, and they too felt that we should go for this challenge.

Why did we feel we had to do this? First, we are convinced of the importance of having a journal devoted to internal medicine that is based in the Netherlands. Such a journal provides a clinical and scientific forum for exposure of the high quality of this speciality in the Netherlands. This immediately raised the question: should that journal be in English? We had no doubts about that. The contents of the Journal are not only relevant for Dutch internists and clinical investigators, but also for their international colleagues. It is clear from the increased impact factor, as discussed by Professor Hoepelman in his farewell editorial,[1] that there is a growing international interest in the Journal. It is our overriding ambition to increase its status internationally. We are convinced that there is a niche for the Journal among the international medical journals. To fill that niche the editors will work very hard to attract papers that fit our mission statement, 'To serve the need of the internist to practice up-to-date medicine and to keep track with important issues in health care. With this purpose we publish editorials, original articles, reviews, controversies, consensus reports, papers on speciality training and medical education, book reviews and correspondence.'
To accomplish this, we have approached a number of enthusiastic and renowned colleagues from the Netherlands and abroad, to join the editorial board.

The change of the editorial board's location has had quite an impact on the Journal, but this is partly a coincidence. Shortly before the move of the Journal's editorial board to Nijmegen, the board of the Netherlands Association of Internal Medicine (NIV) decided to switch to another publisher. This change was a good opportunity for the new editors and the new publisher to think about the format and layout of the Journal. With these changes we also appointed a new editorial assistant, Ms Geeralien Derksen-Willemsen. With some pride we present the first issue of Volume 60. On the cover you will find the new logo and also a reprinted mezzotint by the Dutch artist Caroline Koenders. We intend to reproduce contemporary Dutch graphic art on the cover of coming issues. Our aim is to draw attention to the superb quality of this type of art in the Netherlands, and we will give our readers the opportunity to buy the original prints at a reasonable price (as long as the edition permits). On page 25 you will find details about this month's artist and how to order.

We hope that our readers will be as enthusiastic about our renewed Journal as we are.
On behalf of the editors,

Jos W.M. van der Meer
Editor in chief

Reference

1. I.M. Hoepelman. Editorial. The Netherlands Journal of Medicine: end of a fruitful period and a new start. Neth J Med 2001;59:267-9.

Netherlands
The Journal of Medicine

REVIEW

Statins and the stroke-cholesterol paradox

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ABSTRACT

Although strokes belong to the group of cardiovascular disorders, there is no clear association between LDL and/or HDL levels and 'stroke' as an entity. However, there is ample evidence that statins reduce stroke risk in selected patient groups such as survivors of myocardial infarction. This apparent paradox can be explained on the one hand by the heterogeneity of strokes as a group and on the other hand by the specific characteristics of statins. There are strong indications for a relationship between blood lipid profiles and types of stroke that have atherosclerosis as the underlying pathogenetic mechanism. Apart from their ability to reduce LDL levels significantly, statins have a number of other properties, which influence the process of atherosclerosis at various stages. Future and ongoing trials have to prove which patients at risk for stroke will benefit most from the preventive use of statins.

INTRODUCTION

Cerebrovascular disease is one of the leading causes of death worldwide and responsible for long-term disability in many patients.[1] More than 30,000 strokes are diagnosed each year in the Netherlands and an increase of 35-40% in the number of patients is predicted for the year 2015.[2] Although stroke is considered to be a vascular disorder, many epidemiological studies failed to demonstrate an association between blood cholesterol levels and the incidence of stroke.[3] Furthermore, no reduction in the risk of stroke could be established in a large number of trials of cholesterol lowering through diet and various agents. These data may suggest no involvement of lipid metabolism in the pathogenesis of stroke, but recent clinical trials and meta-analyses of the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in patients with a history of coronary artery disease have clearly shown a reduction in stroke risk. This apparent discrepancy raises questions about the interpretation of the epidemiological data, the pathogenesis of stroke and the mode of action of statins. Furthermore, from a clinical point of view, several questions arise. Which patients will benefit from cholesterol lowering and/or statin therapy and will the effect persist when statin treatment is combined with other agents that reduce stroke risk, such as ACE inhibitors and the newer antiplatelet drugs?[4,5]

POSSIBLE EXPLANATIONS FOR THE 'STROKE-CHOLESTEROL PARADOX'

Although it is well established that there is no association between LDL and/or HDL levels and 'stroke' as an entity, there is also ample evidence that statins, i.e. cholesterol-lowering therapy, reduce stroke in selected patient groups. Several explanations may be given for this paradox. In the first place 'stroke' is not one unequivocal entity but a collection of cerebrovascular diseases (*figure 1*). It may well be that the 'strokes' registered in the epidemiological studies differ from the 'strokes' observed in the large statin interventional studies.[6,7] Secondly, the epidemiological data may be flawed as to the type of stroke that may be related to cholesterol. It is well known that coronary atheroma, i.e. large-vessel disease, is cholesterol related

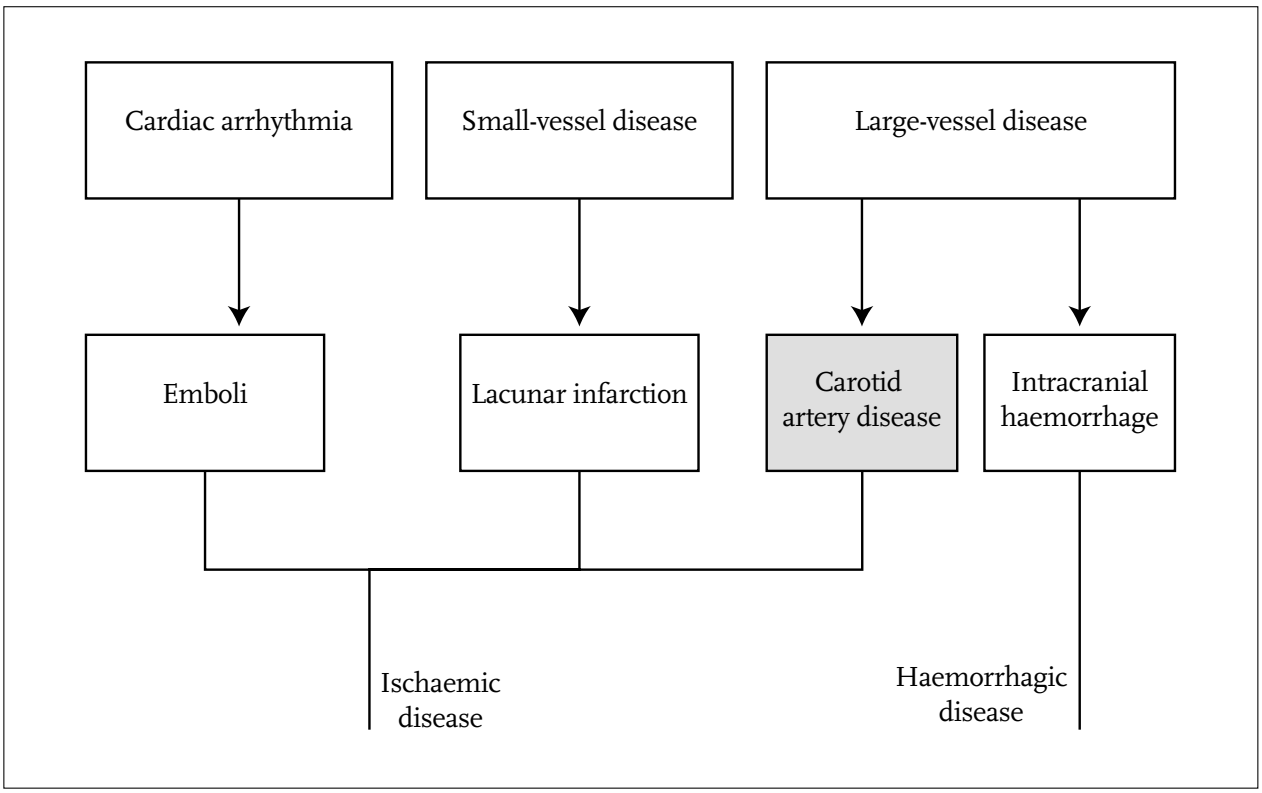

Figure 1

Tentative classification of the types of stroke

Diseases and organ damage leading to the clinical syndrome of stroke are tentatively classified. Ischaemic and haemorrhagic diseases are discriminated. The box of stroke type implicated as cholesterol-related is emphasised.

and is the main cause of coronary heart disease. Carotid atheroma on the other hand is only one of the several causes of cerebrovascular disease (*figure 1*). Furthermore, the age at which patients develop stroke is much higher than it is for CHD. Therefore, the number of patients that could have developed cholesterol-related stroke is diminished by the time they are old enough because of the mortality associated with CHD. This theory is in keeping with the finding that when patients known to have (survived) large-vessel disease (atheroma) are selected, i.e. patients that have already had an MI, they not only run a higher risk for a second MI but also for a subsequent stroke.[8, 9] Finally, a completely different explanation for the stroke-cholesterol paradox may lie in the pleiotropic effects that statins may have in addition to their ability to lower cholesterol.

Epidemiology and types of strokes

Conflicting data from individual stroke studies and from population-based observations have turned the relationship between serum cholesterol and stroke incidence into a controversial issue. Some of the studies show a positive association, some no association and others, including Framingham, even a negative one.[10] A review of 45 prospective observational cohorts involving 450,000 individuals with a mean follow-up of 16 years (total 7.3 million person-years of observation), recording 13,397 participants as having had a stroke, could not demonstrate an association between blood cholesterol and stroke.[11] However, because data on the types of strokes were not centrally available, the authors stated that the lack of an overall relation did not exclude a positive association of cholesterol with ischaemic stroke (see *figure 1*). In fact, such a positive association between serum cholesterol level and non-haemorrhagic stroke was observed in the Multiple Risk Factor Intervention Trial (MRFIT) registering six-year mortality rates in 350,977 middle-aged men.[12] Interestingly, that same study showed an inverse association of the serum cholesterol level with the risk of death from intra-cranial haemorrhage, although this was confined to men with diastolic blood pressure ≥90 mmHg. Support for a positive association of cholesterol with non-haemorrhagic cerebrovascular events comes from the Copenhagen City Heart Study and from the Eastern Stroke and Coronary Heart Disease Collaborative Group.[13, 14] In the Copenhagen City Heart Study the effect was found only in the group with cholesterol levels >8 mmol/l, corresponding to the upper 5% of the distribution in the study population.[14] This Danish study following 19,698 individuals for more than ten years and observing 660

non-haemorrhagic and 33 haemorrhagic events, also showed a negative association between high-density lipoprotein (HDL) cholesterol and risk of non-haemorrhagic events.
So whether or not an association is demonstrable may be related to the type of cerebrovascular event. It has been suggested that the positive association between increasing cholesterol and atherosclerosis-related stroke is diluted by a weaker association with ischaemic stroke due to intra-cranial small-vessel disease (lacunar disease) and counterbalanced by a negative association with haemorrhagic stroke (see also *figure 1*).[13] This finding is in agreement with Haffner's data showing that patients known to have (survived) large-vessel disease, i.e. patients that have already had an MI, not only run a higher risk for a second MI but also for a subsequent ischaemic stroke.[8, 9]

Cholesterol-lowering trials and stroke: non-statin trials
Once cholesterol was recognised as a risk factor for atherosclerosis, clinical trials were started to reduce blood cholesterol levels either by diet alone or combined with a drug. Most of the trials were designed to assess the effects of lipid lowering on coronary heart disease and not on cerebrovascular disease. A meta-analysis of these trials from the 'pre-statin' era revealed no significant reduction in all (fatal and non-fatal) stroke risk or fatal stroke risk.[15] However, with the primary endpoint being a coronary event, the number of patients in most of these trials was small and the incidence of strokes low.
Furthermore, the reduction in cholesterol level in the treated as compared with the control subjects was limited.[16] Recently, the results of the Veterans Affairs Cooperative Studies Programme High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) were published.[17] This secondary prevention trial focused on patients with a history of coronary heart disease and low HDL-c levels (<1.0 mmol/l), who were treated either with gemfibrozil or a placebo. The median follow-up was 5.1 years. In addition to a 22% reduction in non-fatal myocardial infarction, treatment resulted in a 29% risk reduction in investigator-designated stroke ($p<0.04$), 25% reduction in confirmed stroke ($p<0.10$) and a 59% reduction in transient ischaemic attacks (TIA) ($p<0.001$).

Cholesterol-lowering trials and stroke: statin trials
One of the first large trials showing impressive data on the effectiveness of statins to reduce risks related to atherosclerotic disorders was the Scandinavian Simvastatin Survival Study (4S).[6] In this trial of coronary patients with elevated levels of blood cholesterol, treatment reduced the overall incidence of stroke by 29%. The highest reduction was observed in non-embolic stroke and TIAs. A more detailed analysis of the effect of statin treatment on stroke incidence in patients with a history of coronary heart disease was performed as part of the Cholesterol And Recurrent Events (CARE) study.[18] During a median follow-up period of five years, 4159 subjects with a recent myocardial infarction and mildly elevated total- and low-density lipoprotein (LDL) cholesterol were studied. A total of 128 strokes (52 on pravastatin, 76 on placebo) and 216 strokes or TIAs (92 on pravastatin, 124 on placebo) were observed, representing a 32% reduction in all-cause stroke and 27% reduction in stroke or TIA. All categories of strokes were reduced and there was no increase in haemorrhagic stroke.
Another more detailed analysis on stroke risk was made in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study.[19] Pravastatin was compared with placebo in 9014 patients with a history of myocardial infarction or unstable angina and total cholesterol ranging from 4.0-7.0 mmol/l. Among the patients given placebo, the risk of stroke was 4.5%, as compared with 3.7% among those given the drug (relative reduction in risk: 19%). The risk reduction was somewhat higher (23%) in the subgroup of non-haemorrhagic stroke and again there was no negative effect on haemorrhagic stroke.
Apart from these secondary prevention trials, a number of meta-analyses have now been published. They conclude that treatment with statins reduces the risk of stroke by 27-31% with the most pronounced effect in patients who have had a previous myocardial infarction (32%) and a (non-significant) 11-20% reduction in primary prevention trials.[10, 20] In one of the most recent and extensive meta-analyses, Bucher and colleagues reviewed all randomised-controlled trials of any cholesterol-lowering therapy that provided data on non-fatal and fatal strokes, on death from coronary heart disease, and on overall mortality.[21] This analyses included 28 trials with over 49,000 and 56,000 patients in the intervention and control groups respectively. Treatment with a statin resulted in a risk ratio for non-fatal and fatal stroke of 0.76. In contrast, the risk ratios with fibrates, resins, and dietary modification were all close to 1.0, meaning no effect on the incidence of stroke. All these data point to a discrepancy between the results from statin studies and those from earlier observational studies and non-statin interventions. One explanation for this finding is, of course, the difference in the degree of cholesterol lowering produced by the statins as compared with non-statin regimens.

HMG COA REDUCTASE INHIBITORS

The effectiveness of statins in stroke reduction without an apparent association between stroke and cholesterol has become an intriguing subject of debate in medical literature and even a polemic in the Lancet.[22-26] Crucial to the discussion is the recognition that stroke is not a single disease but rather a collection of cerebrovascular disorders

with different pathogenesis (*figure 1*). Risk factors are numerous and may vary with age and type of event. Since the elderly suffer the highest rates of strokes, risk factors in this group will strongly influence epidemiological data. Such risk factors in the elderly were examined in the Cardiovascular Health Study.[27] Apart from age, a history of hypertension, use of antihypertensive drugs, and systolic (but not diastolic) blood pressure were associated with the risk of stroke. History of diabetes and several measures of target organ disease, such as abnormal left ventricular wall motion and increased left ventricular mass, carotid stenosis, and atrial fibrillation, also predicted stroke risk.[28] Epidemiological studies that only focus on overall stroke incidence may miss the link between cholesterol and the type of stroke related to atherosclerosis because a number of patients at high risk for the atherothrombotic type of stroke are likely to die from a coronary event before even having the chance to develop a stroke. So, as Rosendorff stated, the most intriguing aspect of the paradox is not the effectiveness of statins in reducing stroke risk but the failure of other lipid-lowering interventions to do so.[22] This can largely be explained by the relative paucity of the non-statin trials.[10] There have been only five pre-statin secondary prevention trials, and of these only two recorded sufficient numbers of strokes to provide information about the effects of cholesterol lowering and stroke prevention. In one of them, the Coronary Drug Project, niacin treatment was associated with a significant 24% reduction in stroke not observed in the clofibrate arm of the study.[29] The majority of the earlier trials included relatively healthy individuals without a history of coronary heart disease in whom also statins would fail to reduce stroke risk as shown in the primary prevention studies. Furthermore most of the studies had coronary heart disease mortality as primary endpoint and did not examine stroke at all. Study participants were generally younger with lower stroke risk profiles.

Although the effectiveness of statins is no longer debated, there is still considerable discussion on how statins influence the pathogenesis of atherothrombotic disorders. Theories range from simple LDL cholesterol reduction and lipid profile modification to a wide spectrum of so-called pleiotropic effects (*table 1*).

Table 1
Experimental effects of statins which could play a role in the observed stroke protection

Lipid metabolism
Reduction LDL
Increase HDL
Decrease TG
Plaque dynamics
Regression
Stabilisation
Retardation progression
Inflammation/proliferation
Anti-inflammatory action
Reduced neutrophil and monocyte adhesion
Reduction of VCAM-1 and ICAM-1 expression
Reduced smooth muscle cell proliferation
Haemostatic balance
Reduced platelet aggregation
Tissue factor modification
Enhancement of fibrinolysis
Blood pressure
Increase effects of antihypertensives
Endothelial dysfunction
NO synthase upregulation
Decrease endothelin-1 levels

Modes of action of statins

Statins, as inhibitors of the enzyme HMG CoA reductase, are able to lower the synthesis of LDL cholesterol. However, most of them also have the potency to decrease the concentration of triglycerides and to increase serum HDL cholesterol. This modification of lipid metabolism may reduce the risk of stroke by plaque regression or retardation of plaque progression, by plaque stabilisation and indirectly by influencing cardiac events.[10] By reducing the incidence of coronary artery disease related disorders as myocardial infarction, coronary bypass surgery, atrial fibrillation and left ventricular dysfunction statins reduce the risk of stroke since all of these are themselves associated with cerebrovascular events.

Apart from the risk factors already mentioned, a strong association of extracranial carotid intimal medial thickening with incident stroke is now well recognised.[28] Several studies using B-mode ultrasound have shown that cholesterol lowering retards the progression of carotid atherosclerosis, which favours the application of statins.[30-32] However, based on the experiences of intervention trials in coronary heart disease, it is now generally accepted that plaque stabilisation is a more important mechanism in risk reduction than plaque regression. Clinical benefit from statins can already be observed relatively soon after initiation of therapy while it takes much longer to demonstrate plaque regression or inhibition of progression.[33] Although much of the plaque modifying effect may be

directly linked to statin-induced changes in lipid metabolism, that is probably not the whole story. In the West of Scotland Coronary Prevention Study (WOSCOPS), a primary intervention trial with pravastatin in middle-aged men with slightly elevated cholesterol levels, treated individuals had a better prognosis compared with controls despite the same lipid profile (total cholesterol, LDL-c, HDL-c and triglycerides) suggesting an additional benefit from the statin.[7]

At the moment quite an impressive list of these non-lipid, pleiotropic effects of statins can be made up including effects on inflammation and the immune system, smooth muscle cell proliferation, macrophage metabolism, collagen synthesis and oxidation of LDL cholesterol (*table 1*).[34] Statins also influence the haemostatic balance with effects on platelet aggregation, expression of tissue factor, plasma levels of fibrinogen and on fibrinolysis. Treatment with statins can lower blood pressure, a mechanism that would be immediately relevant with regard to stroke protection.[23] One of their most intriguing abilities is to improve endothelial dysfunction, which has been shown both in *in vitro* and *in vivo* models. Already within a month, treatment with simvastatin in hypercholesterolaemic patients augments both the stimulated and basal nitric oxide (NO) dilator functions of the endothelium, an effect that persists with continued therapy.[35, 36] In an animal model of occlusion, reperfusion of the middle cerebral artery, augmentation of cerebral blood flow, reduction of cerebral infarct size and improvement of neurological function were demonstrated in statin-treated animals.[37] This effect was not associated with cholesterol lowering but with up-regulation of endothelial NO synthase. So, apart from reducing stroke risk, the statin class of drugs exhibits a number of properties that are likely to attenuate the effects of ischaemia on the brain vasculature and parenchyma. Although these data are extremely interesting and promising, we should realise that many of them derive from laboratory experiments and animal studies and that their clinical relevance needs to crystallise. Furthermore, while cholesterol lowering is a class effect of statins, there may be essential differences between the statins with regard to the various pleiotropic effects.[38]

CONCLUSION

The relationship between cholesterol and stroke is still controversial although there are indications that an increase in cholesterol is associated with a higher incidence of non-haemorrhagic stroke. There is now clear evidence that statins reduce the risk of stroke in patients with a previous myocardial infarction. This effect may be mediated by modification of lipid metabolism, but also non-lipid related plaque stabilisation, improvement of endothelial dysfunction and neuroprotective effects are possible mechanisms. At the moment several large secondary trials are ongoing to evaluate the recurrence risk in patients with a previous stroke. Very recently, results of the Medical Research Council/British Heart Foundation Heart Protection Study have been presented at the American Heart Association's 2001 meeting showing that five years of statin treatment prevents heart attacks, strokes or other major vascular events in 70 of every 1000 patients who have previously had a stroke.[39] Since stroke prevention may be extremely relevant in the elderly population, new trials like the Risk Evaluation and Stroke Prevention in the Elderly-Cerivastatin Trial (RESPECT) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) will focus on older individuals at risk. These data will help us to answer the question which patients will benefit most from treatment as well as to make adequate cost-benefit calculations. In the mean time, useful guidelines have been supplied by the recent stroke consensus of the Dutch Heart Foundation (Nederlandse Hartstichting) and the Dutch Institute for Health Care Improvement CBO.[2] In patients with a mild stroke, treatment with a statin is recommended in women younger than 75 years of age and men younger than 70 with a manifestation of atherosclerosis, such as symptomatic carotid stenosis, a recent myocardial infarction, angina or peripheral vascular disease, unless plasma cholesterol level is <5 mmol/l or LDL cholesterol <3.2 mmol/l. If there is no atherosclerosis but instead high blood pressure, diabetes or a family history of premature atherosclerosis, treatment should be based on the risk of the development of coronary artery disease. The near future will tell whether this policy has been adequate.

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ORIGINAL ARTICLE

Cardiovascular abnormalities in patients with a carcinoid syndrome

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ABSTRACT

Background: Heart failure is an important reason for morbidity and mortality in patients with carcinoid. Carcinoid heart disease is caused by increased levels of circulating serotonin. Because carcinoids also produce catecholamines, we evaluated cardiovascular manifestations of autonomic dysfunction in patients with a carcinoid syndrome.

Methods: Twenty patients with a midgut carcinoid, who had a carcinoid syndrome with a median duration of 72 months, and markedly elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion were studied.

Results: Ten patients had no symptoms of heart failure, i.e. New York Heart Association (NYHA) functional class I, 6 had class II, and 4 class III heart failure. Transthoracic echocardiography (TTE) showed right-sided valvular abnormalities in 13 of 19 evaluable patients (mild n=8, severe n=5). Fourteen of the 20 patients (70%) had an elevated concentration of plasma N-terminal atrial natriuretic peptide (N-ANP), which correlated with NYHA class, TTE abnormalities, and increased urinary metanephrine excretion. Heart rate variability (HRV) parameters, in particular those associated with increased sympathetic activity (low frequency power, p=0.002 versus healthy individuals), were impaired but were independent of NYHA class and TTE findings and correlated with urinary metanephrine excretion (r=-0.49, p<0.05).

Conclusion: In these 20 carcinoid patients with substantial secretory activity of the tumour, overt cardiac morphological changes were present in a minority of patients. However, N-ANP values and HRV profile were markedly abnormal, and related to enhanced urinary excretion of catecholamine and metabolites, suggesting autonomic derangement. These abnormalities possibly herald the development of more severe cardiac dysfunction and may be indicative of the need for preventive drug treatment.

INTRODUCTION

Heart failure is an important cause of death in patients with a carcinoid syndrome.[1-3] In carcinoid heart disease plaques are deposited on the endocardium, leading to tricuspid valve insufficiency, pulmonary valve stenosis,[4] and subsequently right-sided heart failure. In a large study,[3] transthoracic echocardiography revealed tricuspid regurgitation in 56% of 132 patients with a carcinoid syndrome. Although the pulmonary valve was less frequently affected, echocardiography showed retracted pulmonary cusps leading to stenosis as well as regurgitation. The development of carcinoid heart disease is associated with increased urinary 5-HIAA excretion.[2, 3, 5, 6] Although excessive serotonin production is the hallmark of carcinoid tumours, catecholamine secretion is also frequently increased in these tumours.[7, 8] Serotonin[9, 10] and catecholamines[11-13] directly affect cardiovascular function, leading to heart rate disorders, alterations in autonomic control, and catecholamine-induced cardiomyopathy. At present only limited information is available on these functional cardiovascular effects of serotonin and catecholamines in carcinoid patients.[14, 15] With the introduction of new treatment modalities, such as somatostatin

analogues and interferon alpha, serotonin overproduction can be effectively reduced.[16, 17] Patients who had a biochemical response to treatment showed no further deterioration of carcinoid heart disease.[18]
In left-sided, non-carcinoid heart failure, natriuretic peptides[19] and heart rate variability (HRV)[20] are used as early markers of autonomic dysfunction, as both have prognostic value in these patients.[21-23, 20] In right-sided heart failure resulting from pulmonary hypertension, natriuretic peptides were elevated as well.[24]
The aim of the present study is to investigate cardiovascular autonomic function in patients with a carcinoid syndrome. Cardiovascular manifestations of autonomic function were evaluated with plasma N-terminal atrial natriuretic peptide (N-ANP), and ambulatory electrocardiographic (ECG) monitoring with HRV analysis. The relation between these measurements and the degree of clinically observed heart failure, echocardiographic findings and serotonin and catecholamine secreting activity of the tumour was studied.

METHODS

Patients

Between September 1996 and April 1998, 20 patients with a histologically proven midgut carcinoid tumour leading to a carcinoid syndrome[16] underwent cardiovascular examination including the new parameters N-ANP and HRV. Clinical assessment was performed using a standardised questionnaire for symptoms attributable to the carcinoid syndrome, and for cardiovascular symptoms. Patients were categorised in New York Heart Association (NYHA) functional classes for heart failure. Physical examination was focussed on signs of heart failure. A 12-lead ECG and chest X-ray were performed following standard procedures.

Urine and blood samples

The 24-hour urine samples were collected using two L brown polypropylene bottles (Sarsted, Nuembrecht, Germany) containing 250 mg each of $Na_2S_2O_5$ and EDTA, as preservatives. Samples were acidified to pH 4 with acetic acid, before freezing. Venous blood samples were collected in 10 mL Vacutainer Tubes (Becton-Dickinson, Meylan Cedex, France), containing 0.12 ml of 0.34 mol/l EDTA solution, and were immediately put on ice. Platelet-rich plasma was prepared from whole blood within one hour after sampling by centrifugation for 30 minutes at 120 g and 4 °C. $Na_2S_2O_5$ and EDTA were added as preservatives, in final concentrations of about 10 g/l each. Platelet concentrations were measured with a Coulter Counter Model S plus 4 (Coulter Electronics, Hialeah, FL). Samples were stored at -20 °C and analysed within one week after collection. Venous samples of heparinised plasma were stored at -20 °C until determination of N-ANP.

Analytical methods

The serotonin contents of platelet-rich plasma and urine were determined by high performance liquid chromatography (HPLC), with fluorometric detection.[25] Platelet serotonin content (reference range 2.8-5.4 nmol serotonin/10^9 platelets) was calculated by dividing the serotonin concentration in platelet-rich plasma by the concentration of platelets in the plasma. Urinary 5-HIAA concentrations were determined in ether extracts, by HPLC with fluorometric detection.[26] Urinary creatinine concentrations were measured by a picric acid method with a Merck Mega analyser (Merck, Darmstadt, Germany). Urinary 5-HIAA was expressed in μmol/mol urinary creatinine (reference range 0.8-3.8 μmol/mol).[27]
Urinary excretion of the free catecholamines dopamine (reference value <300 μmol/mol creatinine), noradrenaline (<30 μmol/mol creatinine), and adrenaline (<10 μmol/mol creatinine) was determined by HPLC with electrochemical detection.[28] The free and conjugated catecholamine metabolites 3-methoxytyramine (37-167 μmol/mol creatinine), normetanephrine (71-260 μmol/mol creatinine), and metanephrine (26-69 μmol/mol creatinine) were determined in lyophilised urine samples by stable isotope mass fragmentography.[29]
Plasma N-ANP (reference value 150-500 pmol/l) was measured using a radioimmunoassay obtained from Biotop, Oulu, Finland.[30]

Echocardiography

Transthoracic echocardiography was performed in all carcinoid patients using two-dimensional techniques with colour flow imaging. A standard left parasternal view and an apical four-chamber view were performed. Special attention was given to valve abnormalities and signs of right heart failure: right atrial enlargement, and distension of the inferior caval vein. All echocardiographic investigations were interpreted by one experienced cardiologist (MPB). The patients were classified into three groups according to the echocardiographic results. Group I patients had a normal echocardiography. Patients in group II had one of the following criteria: tricuspid regurgitation, right atrial enlargement, or inferior caval vein collapsing less than 50% of maximal diameter during inspiration. Patients in group III fulfilled two or three of these criteria. A comparable grading system was previously used by Lundin *et al.*[31]

Heart rate registration and heart rate variability

Ambulatory 24-hour ECG monitoring was performed in all patients using Marquette 3 channel AM recorders (8500 series, Laser System, Marquette Electronics Inc.,

Milwaukee, WI).[32] The number of (supra)ventricular premature beats, and (supra)ventricular tachycardias was calculated. For HRV analysis we used a Holter analysis system (Marquette series 8000). Patients with recordings with over 15% of noise or ectopic beats were excluded from evaluation. Time domain parameters as well as the frequency domain parameters low frequency power (0.04-0.15 Hz), high frequency power (0.15-0.40 Hz), and total power were calculated. From a pre-existing large database 20 healthy individuals, matched for age and sex to the carcinoid patients, were selected to constitute a reference group.

Statistics

Values of urinary excretion of catecholamines and metabolites were expressed as multiples of the upper reference value. Other than normal distributions were normalised with logarithmic transformation. Differences between variables were evaluated using Student's T-test when normally distributed, otherwise the Mann-Whitney U test was used. To evaluate relations between variables with normal distribution, we used Pearson's correlation test. For non-normal distribution Spearman's correlation test was used. Multivariate analysis was performed with best subset analysis and stepwise regression. Age, duration of the carcinoid syndrome, HRV parameters, urinary excretion of 5-HIAA and catecholamine (metabolites), and plasma N-ANP were entered as variables in the multivariate analysis. P values <0.05 were regarded as significant.

Table 1
Patient characteristics

Number	20	
Male : female	9 : 11	
Median age in years (range)	57.5	(43-74)
Median duration of carcinoid syndrome	72	(9-154)
Patients with liver metastases	17	
Serotonin metabolism		
Urinary 5-HIAA (median, range)*	16.5	6.7-200.1
Platelet serotonin (median, range)**	30.1	17.8-41.9
Treatment		
Somatostatin analogue	11	
Somatostatin analogue + interferon	3	

** reference range 0.8-3.8 µmol/mol creatinine, ** reference range 2.8-5.4 nmol/10⁹ platelets*

Table 2
Urinary catecholamines

	MEDIAN	RANGE
Dopamine	125.5	34.2-283.4
3-Methoxytyramine	188.5	75.0-704.0
Noradrenaline	19.5	10.8-75.7
Normetanephrine	127.0	74.0-534.0
Adrenaline	2.1	0.1-5.8
Metanephrine	66.5	24.0-143.0

expressed in µmol/mol creatinine

RESULTS

Clinical characteristics

Twenty consecutive patients with a carcinoid syndrome secondary to metastasised midgut tumours were analysed. Baseline characteristics are presented in *table 1*. Ten patients (50%) had symptoms of heart failure; dyspnoea (n=4), ankle oedema (n=4), orthopnoea (n=1) and nycturia (n=5). Of these ten patients, six had NYHA class II, and four class III heart failure. Nine of the 20 patients experienced episodes of palpitations. On physical examination, seven of 20 patients had a precordial murmur, three had an elevated central venous pressure, and four had oedema of the lower extremities. In one patient the ECG showed a right bundle branch block. ECG was normal in the remaining 19 patients. Chest X-ray revealed no cardiovascular abnormalities.

Echocardiography

Echocardiography was normal in six patients (group I). In eight patients mild echocardiographic abnormalities were detected (group II): tricuspidal insufficiency (n=3), right atrial enlargement (n=3), and distension of the inferior caval vein (n=2). Five patients had signs of severe carcinoid heart disease on echocardiography (group III): tricuspidal insufficiency and right atrial enlargement (n=2), tricuspidal insufficiency and distension of the inferior caval vein (n=2), in one patient echocardiography showed tricuspidal insufficiency, right atrial enlargement, and a distended inferior caval vein. In one patient transthoracic echocardiography was technically impracticable. None of the 20 patients showed left-sided cardiac abnormalities.

Markers of serotonin metabolism

No differences between the respective echocardiographic subgroups or NYHA classes were observed for urinary 5-HIAA excretion or the duration of the carcinoid syndrome, i.e. the time of exposure to elevated serotonin levels. Platelet serotonin was higher in patients with NYHA class II and III heart failure compared with those without heart failure (32.4 versus 27.5 nmol/10⁹ platelets, p=0.04).

Urinary catecholamines and metabolites

Values for urinary excretion of catecholamines and metabolites are presented in *figure 1*; exact values are shown in

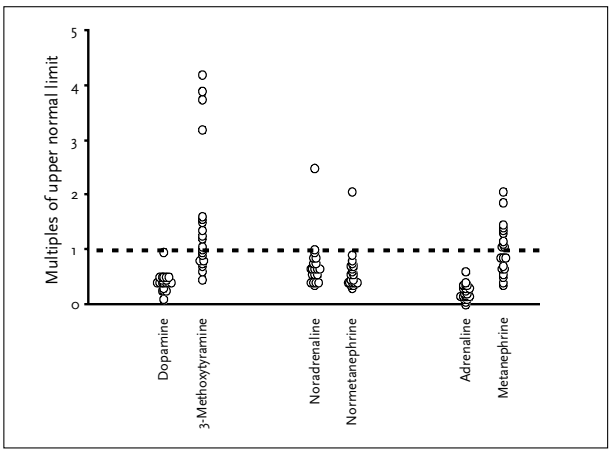
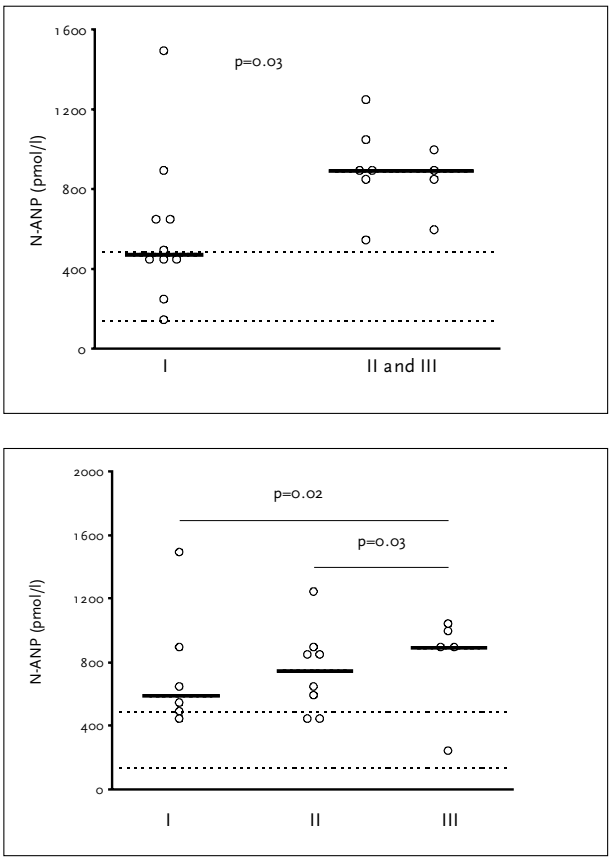


Figure 1

Urinary catecholamine excretion in 20 carcinoid patients expressed as multiples of the upper reference limit. Catecholamines are classified as dopamine (DA) and its metabolite 3-methoxytyramine (3-MT), noradrenaline (NA) and its metabolite normetanephrine (NMN) and adrenaline (A) and its metabolite metanephrine (MN). The horizontal dotted line represents the upper reference limit.



Figures 2a and b

Plasma N-terminal atrial natriuretic peptide (N-ANP) levels in 20 carcinoid patients classified by NYHA functional classes for heart failure (a) and echocardiographic criteria (b). The horizontal dotted lines indicate the upper and lower limit of normal; the drawn lines are medians of the respective subgroups of patients.

table 2. No differences in urinary catecholamine excretion were observed when comparing patients categorised according to NYHA class for heart failure or echocardiographic findings.

N-terminal atrial natriuretic peptide

Plasma N-ANP was elevated in 14 (70%) patients, median concentration was 735 pmol/l (range 153-1484). The ten patients with symptoms of right heart failure had higher levels of N-ANP (p=0.03, *figure 2a*). Although plasma N-ANP did not correlate with right atrial diameter, higher levels were present in patients with echocardiographic evidence of advanced carcinoid heart disease (group III), compared with group I (p=0.02), and group II (p=0.03, *figure 2b*). Plasma N-ANP correlated with urinary metanephrine excretion (r=0.48, p<0.05, *figure 3a*), but not with platelet serotonin and urinary 5-HIAA.

Ambulatory ECG monitoring

Ambulatory 24-hour ECG monitoring revealed no sustained tachycardias. The rates of (supra)ventricular extrasystoles were comparable between recordings of carcinoid patients and of age and sex matched healthy individuals. The rate of (supra)ventricular extrasystoles was not higher in patients with a history of palpitations.

Heart rate variability

A reliable HRV analysis was not possible in one patient because of ectopic beats and noise exceeding 15% of registration time. Time domain and frequency domain parameters for HRV were diminished in 14 of 19 (74%) evaluable carcinoid patients compared with reference values obtained from age and sex matched healthy individuals (*table 3*). No difference in HRV parameters was found between groups of patients categorised according to NYHA class or echocardiographic abnormalities. Low frequency power correlated negatively with urinary metanephrine excretion (r=-0.49, p<0.05, *figure 3b*). The relation of total power (r=-0.42, p<0.05) and high frequency power (r=-0.38, NS) with urinary metanephrine excretion is not shown.

Multivariate analysis

Best subset analysis and stepwise regression showed urinary metanephrine excretion as an independent determinant for low frequency power. Neither urinary 5-HIAA nor the duration of the carcinoid syndrome contributed in the observed variance of low frequency power.

DISCUSSION

In the present study we evaluated carcinoid patients who were at high risk to develop carcinoid heart disease, because of long-lasting exposure to high levels of plasma serotonin.

Table 3
HRV parameters in carcinoid patients versus healthy controls

	CARCINOID		CONTROLS		P VALUE*
	MEDIAN	RANGE	MEDIAN	RANGE	
Mean RR	803	571-985	832	637-1012	NS
SD RR	118	74-176	138	98-226	NS
SDANN	106	65-164	127	85-191	NS
SD	45	18-102	59	37-97	0.019
rMSSD	22	9-125	32	14-53	0.020
pNN50	2.8	0-55	6.7	0.8-26	0.009
Total power	29	11-80	37	24-58	0.006
Low frequency	17	5-47	24	14-35	0.002
High frequency	8	3-43	12	6-22	0.026

* *Mann-Whitney test*

Echocardiography detected overt carcinoid heart disease in only five of 19 (26%) of patients. In contrast to this low incidence of morphological abnormalities, elevated N-ANP values and impaired HRV parameters were present in the majority of the patients as early signs of cardiovascular dysfunction.
Plasma N-ANP levels were elevated in 70% of our patients, indicating right atrial distension.[19] Plasma N-ANP levels correlated with higher NYHA classes, and with the degree of echocardiographic abnormalities. In a study by Lundin *et al.*[31] plasma ANP was elevated only in patients with echocardiographic evidence of advanced carcinoid heart disease, and had prognostic significance for survival. In our study, however, N-ANP was elevated even in patients with symptomatic heart failure who had a normal echocardiogram. Although some carcinoid tumours have the ability to produce ANP themselves,[33] the correlation with NYHA class heart failure and echocardiography, observed in the present study, suggests an atrial source of N-ANP. In addition, N-ANP values correlated with the excretion of metanephrine and not with urinary 5-HIAA excretion. Our data show that clinical heart failure and elevated N-ANP levels probably precede the development of morphological abnormalities detectable with echocardiography.
Our carcinoid patients had impaired HRV parameters. A decrease in low frequency power, associated with elevated sympathetic activity,[34] was observed in 64% of patients. No differences in HRV parameters between the respective NYHA classes or echocardiographic subgroups were found. Impairment of HRV parameters correlated negatively with urinary metanephrine excretion (*figure 3b*). In contrast, no relation between HRV and serotonin production was found. Therefore, autonomic derangement in the carcinoid syndrome, as documented by HRV measurement, might be an early manifestation of cardiovascular involvement distinct from carcinoid heart disease occurring as a late complication of the carcinoid syndrome.
In pheochromocytoma, a tumour also characterised by excessive catecholamine production, a HRV pattern analogous to our findings has been reported.[35] Recent studies

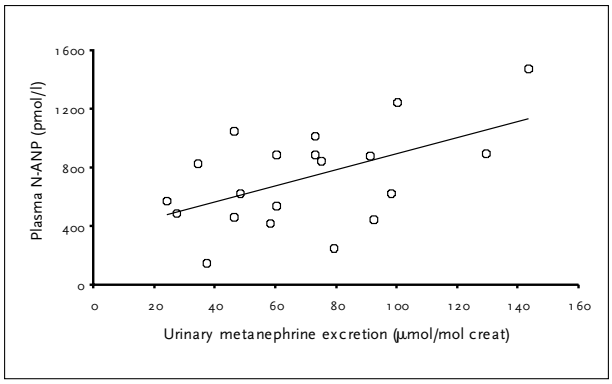


Figure 3a
Relation between plasma N-terminal atrial natriuretic peptide (N-ANP) and urinary metanephrine excretion. Pearson, r=0.48, p<0.02.

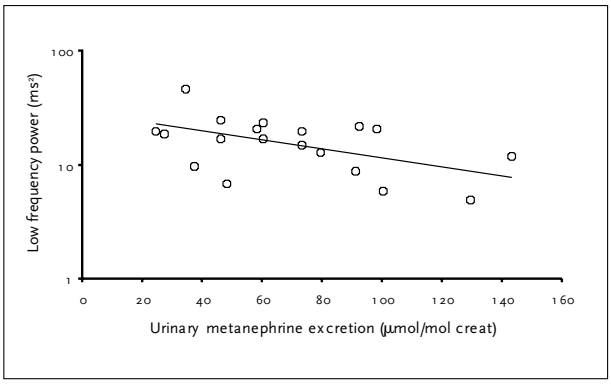


Figure 3b
Relation between low frequency power (note the logarithmic scale) and urinary metanephrine excretion. Pearson, r=-0.49, p<0.05.

describe impaired HRV parameters in carcinoid patients,[36] and an adverse prognosis when combined with carcinoid heart disease.[37] In accordance with our results, no differences were recognised between patients with or without echocardiographic evidence of carcinoid heart disease. This suggests that a decrease of HRV parameters is an early event in patients with a carcinoid syndrome.

Catecholamines probably have a role in the observed autonomic dysfunction. In non-carcinoid heart failure, cardiovascular stress leads to increased adrenal production of catecholamines.[38] In carcinoid patients the tumour can be an additional source of catecholamines as documented in previous studies.[7, 8] Since serotonin release by carcinoid tumours is enhanced by catecholamines,[39] a positive feedback loop can result from cardiovascular stress, leading to a higher tumour secretion rate of serotonin and catecholamines and subsequently a further derangement of cardiovascular function. Catecholamine antagonists, somatostatin analogues and interferon alpha can interrupt this feedback loop. Of special interest is the serotonin type 2 receptor antagonist ketanserin.[40, 41]

The low incidence of valvular disorders observed in our patients suggests a change in the clinical picture of carcinoid heart disease. Improved control of the secreting activity of the tumour by somatostatin analogues delays the development of carcinoid heart disease.[18] The possibility to prevent heart failure by the early institution of somatostatin analogues, interferon alpha or catecholamine antagonists needs further exploration. Furthermore, longitudinal studies evaluating the prognostic value of N-ANP and HRV for the development of heart failure in carcinoid syndrome are needed.

Acknowledgment

We would like to thank Marcel Volmer for his statistical advice.

Note

Professor Van Veldhuisen is an Established Investigator of the Netherlands Heart Foundation (Grant D97.017).

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Failure patterns of combined modality treatment in lung cancer: the impact of staging

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ABSTRACT

Background: Patients with locally advanced non-small cell lung cancer (NSCLC) may be treated with induction chemotherapy (IC) followed by surgery with curative intent. The impact of staging inaccuracies on the failure rate of this intensive combined modality treatment approach, i.e. non-curative chemotherapy and thoracotomy, requires further investigation.

Methods: The records of a cohort of 38 consecutive NSCLC IIIA-N2 patients treated with IC followed by surgery were reviewed.

Results: The clinical course strongly suggested that the standard diagnostic algorithm failed to demonstrate stage IV disease in 34% of the cases. Surgery instigated by CT-based response criteria at restaging after chemotherapy proved to be irradical in 70% of cases.

Conclusion: Our data confirm the limitations of the current work-up of patients with apparently locally advanced NSCLC. This applies to the selection of patients to be assigned to combined modality treatment as well as to the post-chemotherapy assessment of resectability. Improved (re)staging of these patients will enhance the efficiency of intervention trials and prevent patients from being exposed to intensive and toxic therapy from which they derive no benefit.

INTRODUCTION

The only potentially curative treatment for non-small cell lung cancer (NSCLC) is surgery. The survival rate at five years is strongly related to the extent of the disease at diagnosis ranging from 70% for stage IA (T1N0) to 30% for stage IIB (T2N1).[1] In patients without obvious distant metastases, the extent of the mediastinal metastases is a major prognostic factor.[2-4] In a subgroup of these patients, those with resectable, ipsilateral metastastic lymph nodes (stage IIIA), surgery is still a potentially effective approach with five-year survival rates reported between 10 and 30%.[5-8] Evidence is growing that the outcome of patients with locally advanced NSCLC can be improved by treatment with induction chemotherapy (IC) followed by surgery.[9-13] Although the gain in survival for the group is modest, a specific subset of patients, especially those with negative mediastinal lymph nodes (MLN) at surgery after IC[7, 10, 14, 15] clearly benefit from the procedure.
Selection procedures prior to surgery are based on internationally accepted guidelines.[16-19] These staging algorithms are based on results obtained in several retrospective studies in which the majority of patients had NSCLC stage I-II, and were developed before the introduction of combined modality treatment for stage IIIA disease. Therefore, one may question whether these algorithms can also be applied in patients with clinically proven stage IIIA disease who are selected for IC and subsequent surgery.
Here, we analysed in retrospect the outcome of a cohort of stage IIIA-N2 NSCLC patients assigned to combined modality treatment with special emphasis on the value of staging and re-staging techniques.

MATERIAL AND METHODS

Study population

The study group consisted of 38 consecutive patients (26 men and 12 women) with NSCLC stage IIIA-N2, with an average age of 56 years (range 38-74). The initial staging, performed according to the guidelines of the American Society of Clinical Oncology,[16] included computer tomography (CT) of the chest, liver and adrenal glands, mediastinoscopy and if indicated CT or MRI of the brain, bone scintigraphy or ultrasound of the liver. A CT scan of the brain was performed when the patient had signs or symptoms of central nervous system disease. A bone scan was performed when bone pain, chest pain or elevated serum calcium or serum alkaline phosphatase was present. All patients underwent mediastinoscopy and had histologically proven N2 disease. All patients received platinum-based polychemotherapy. Patient characteristics are listed in *table 1*.

Study design

The records were reviewed of a cohort of 38 consecutive patients who, in the period September 1993-March 1998, were diagnosed with NSCLC stage IIIA-N2, and treated with IC followed by surgery in our hospital.

Table 1
Patient characteristics

Total patients	n=38
Age (mean +/- SD)	56 +/- 9 years
Gender	
Male	n=26
Female	n=12
Histology primary tumour	
Adenocarcinoma	n=11
Squamous cell carcinoma	n=18
Large cell carcinoma	n=8
Mixed tumour	n=1
Stage IIIA-N2	
T1N2M0	n=3
T2N2M0	n=24
T2-3N2M0	n=1
T3N2M0	n=10
Response to induction chemotherapy	
PD	n=11
SD	n=9
PR	n=18

SD = stable disease, PD = progressive disease, PR = partial response

Methods

Radiological procedures

CT was performed before and after three cycles of IC in a spiral mode, from the adrenal glands to the supraclavicular region, with a bolus injection of 100 ml contrast medium. Scan delay was 30 seconds. Slice thickness was 10 mm, without interslice gap.

Surgical procedures

In responding and stable patients, thoracotomy with the aim of complete resection was performed. During thoracotomy, resection of the tumour with systematic hilar and mediastinal dissection was performed. Complete resection was defined as macroscopically and microscopically free tumour margins, and the MLN free of tumour. An irradical resection was defined as tumour in the margin of the resected material either macroscopically or microscopically. A patient was found to be irresectable at thoracotomy when the primary tumour could not be resected completely, or when investigation of a frozen section of mediastinal lymph nodes confirmed lymphatic spread.

RESULTS

Of the 38 patients, 15 (39%) did not proceed to surgical treatment (flow chart, see *figure 1*). Progressive disease during IC was observed in the majority of these patients (11/15) while three patients died, two from therapy-related causes.

One patient was lost to follow-up before surgery. Of the remaining 23 patients, one is alive with no evidence of disease (follow-up 52 months), four are alive with disease (median disease-free interval of 29 months, median follow-up 30 months, range 12-62 months), and 18 have died due to the disease.

Initial staging

Distant metastases, undisclosed at initial staging, became apparent in 13 out of 38 patients during IC (n=8) or within six months after surgery (n=5). During IC, six patients had multiple bone metastases of which two had a normal baseline bone scan. Two patients proved to have multiple brain metastases (in one combined with skeletal metastases). Adrenal gland metastasis was discovered in another patient, whose CT scan had been normal at diagnosis. Distant metastases becoming clinically apparent within six months after surgery (n=5) consisted of multiple intracerebral (n=2), extensive skeletal (n=2) and multiple intrapulmonary metastases (n=1) (*table 2*). The initial staging algorithm had not required diagnostic tests aimed at distant metastases in any of the patients with extrapulmonary metastases.

Table 2
Characteristics of patients undergoing thoracotomy

PATIENT	TNM PRIOR TO IC	TNM AFTER IC	RESPONSE TO IC (CT)	PATHOLOGICAL TNM	PATHOLOGICAL COMPLETE RESECTION	FOLLOW-UP*	RECURRENCE/PROGRESSION PRIMARY TUMOUR	METASTASES	DISEASE FREE INTERVAL (MONTHS)
12	T1N2M0	T1N0M0	Partial	T0N1M0	Yes	AWD	No	Recurrent nodal metastases	
13	T2N2M0	TxN0M0	Partial	T0N1M0	Yes	NED	No		
14	T3N2M0	T1-2N0M0	Partial	T1N1M0	Yes	DOD	No	Recurrent nodal metastases	6
15	T2N2M0	T2N2M0	Stable	T2N2M0	No	DOD	No	Brain metastases	6
16	T2N2M0	T1N2M0	Partial	T2N2M0	No	AWD	No	Bone metastases	12
17	T2N2M0	T1N2M0	Partial	T2N2M0	No	DOD	Yes		10
18	T2N2M0	T2N2M0	Partial	T2N2M0	No	DOD	No	Lung metastases	1
19	T2N2M0	T1N2M0	Partial	T1N0M0	Yes	DOD	Yes		8
20	T2N2M0	T1N0M0	Partial	T2N2M0	Yes	DOD	No	Bone metastases	1
21	T2N2M0	T2N0M0	Partial	T2N1M0	Yes	AWD	Yes		29
22	T2N2M0	T1N0M0	Partial	T1N0M0	Yes	DOD	No	Brain metastases	6
23	T2N2M0	T1-2N2M0	Partial	T1-2N2M0	No	DOD	No	Brain metastases	9
24	T2N2M0	T2N2M0	Stable	T4N1M0	No	DOD	No	Skin and Bone metastases	2
25	T2N2M0	T2N0M0	Stable	T4N1M0	No	DOD	No	Skin metastases	7
26	T2N2M0	T2N2M0	Partial	T3N2M0	No	DOD	No	Bone metastases	10
27	T2N2M0	T2N0M0	Stable	T4N2M0		DOD	Yes		
28	T2N2M0	T2N2M0	Stable	T2N2M0		DOD	No	Recurrence tumour in trachea	13
29	T1N2M0	T1N0M0	Partial	T1N2M0		DOD	No	Bone metastases	12
30	T2N2M0	T2N2M0	Partial	T2N2M0		DOD	Yes		
31	T3N2M0	T2N2M0	Partial	T4N2M0		DOD	No	Bone metastases	18
32	T3N2M0	T3N0M0	Stable	T4N2M0		DOD	Yes		
33	T2N2M0	T2N2M0	Stable	T2N2M0		DOD	No	Bone metastases	12
34	T2N2M0	T2N2M0	Partial	T2N2M0		AWD	No	Skin metastases	19

** NED = No evidence of disease, AWD = alive with disease, DOD = death of disease, TNM = stages of bronchuscarcinoma (T = primary tumour, N = lymph nodes, M = distant metastases), IC = induction chemotherapy, CT = computer tomography*

Restaging after induction chemotherapy

At CT scanning of the thorax major tumour response, all partial responses (PR)[19] were found in 18 patients, and stable disease (SD) in nine. In the 23 patients undergoing surgery (*table 3*) a complete surgical resection was achieved in seven (30%). In eight patients, the malignancy was irresectable because of pathologically positive MLN (n=5), T4 lesions (n=2) or combined T4N2 (n=1). In the remaining eight patients, surgical resection was performed but proved to be irradical at pathological examination due to the tumour bearing MLN with extracapsular growth (n=6) and evidence of T4 disease (n=2). Three out of seven patients classified as 'stable disease' by CT criteria had technically resectable disease *versus* 12 of 16 of patients with partial response. On a pathological level, 'stable disease' adequately predicted a negative outcome of resection since none of these patients proved to have a complete resection (*table 3a*). Radiological response poorly predicted the surgical outcome; only seven out of 16 patients with a PR had a complete resection (44%, 95% CI: 20-70%).

Table 3a
CT response criteria versus resectability (microscopical level)

	COMPLETELY RESECTED (PA)	NOT COMPLETELY RESECTED (PA)	TOTAL
CT: PR	7	9	16
CT: SD	0	7	7
Total	7	16	23

Table 3b
CT criteria (1 cm) versus pN2 involvement after chemotherapy

	PN2+	PN0/1	TOTAL
CT: N2+	11	2	13
CT: N0/1	4	6	10
Total	15	8	23

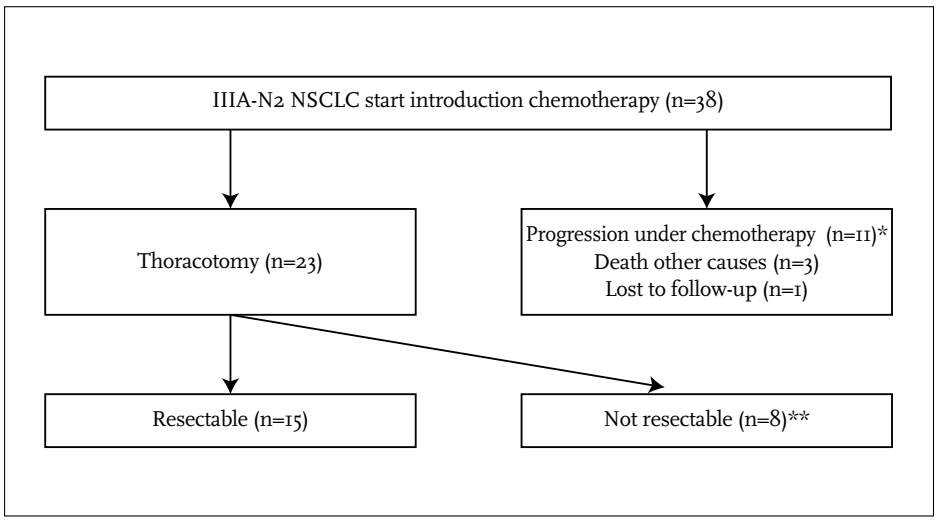

Figure 1
Flow chart study
*** progression under chemotherapy: distant metastases (n=6), progression primary tumour (n=5), ** not resectable at thoracotomy: tumour positive MLN (n=4), T stage (n=3), both N and T stage (n=1)**

With respect to the MLN status at surgery, the majority (15/23) proved to have N2 involvement. A pathological complete remission of MLN metastases was achieved in eight patients (35%, 95% CI: 15-54%) (*table 3b*). Using an MLN size on CT exceeding 1 cm as radiological evidence for MLN involvement, after IC computer tomography incorrectly classified six patients (26%): four falsely as negative and in two the pathological response was underestimated.

DISCUSSION

When considering combined modality treatment in locally advanced NSCLC, the key issues are first 'is the diagnosis of stage IIIA correct?' and if so, later in the process: 'was IC successful to the extent that this patient will benefit from surgical therapy?'
In the study presented here, the clinical course suggested that 34% (13/38) of the IIIA-N2 NSCLC patients had distant metastases at the time of assignment to combined modality treatment. Alternatively, one might argue that these patients suffered from progression of disease despite induction chemotherapy. One way to overcome this problem is by extending the staging guidelines[16] in this specific subset of patients and to perform the complete battery of diagnostic tests in every patient (CT, MRI, bone scan, ultrasound) with a risk for metastatic disease as suggested by Goldstraw in 1994.[17] In addition, novel diagnostic techniques such as whole-body positron emission tomography (PET) should be explored. PET allows for non-invasive imaging and quantification of physiological, biochemical and pharmacokinetic processes *in vivo*. Tumour cells generally demonstrate increased glucose consumption,[20] which can be measured *in vivo* by PET using administration of [^{18}F] fluoro-2-deoxy-D-glucose (FDG), a glucose analogue. FDG PET has been successfully used in the diagnosis of solitary pulmonary nodules and in locoregional and distant staging of lung cancer.[21-25] In an ongoing study exploring the use of PET in IIIA-N2 NSCLC patients in our institution, we found evidence of stage IV disease in 23% of the patients referred for combined modality treatment.[21] Others have reported similar results[26] giving credit to the notion that indeed the patients reported here were understaged at the time of diagnosis. Tumour response to IC is currently evaluated with morphologically oriented imaging techniques or invasively at thoracotomy or re-mediastinoscopy. Assuming that microscopical radicality is prognostically relevant, the label 'stable disease' as defined by CT criteria on the response of the primary tumour, appears to be useful (0% radical resection). However, the predictive value of the PR criterium was poor (44%). With respect to the mediastinal status, the CT scan was incorrect in 26%, assuming that pN1 and pN0 have similar prognostic value. In the subset of patients with partial response of the primary tumour, however, presurgical CT was correct in 82% to predict absence or presence of N2 involvement (13/16). The data presented here suggest that the prognosis of these patients cannot be predicted by the presurgical N2 status at CT. These data corroborate and extend the findings of a previous study[7] in which a lack of correspondence between radiological and pathological response was noted. Residual radiological abnormalities did not exclude pathological response, and radiological response did not guarantee resectability at thoracotomy.
It remains to be shown whether any mode of intensified conventional staging will be beneficial to patients at reasonable costs. Whether the post-chemotherapy mediastinal status as provided by PET will provide clinically relevant data needs to be evaluated, but some studies have been promising.[25,27] Unlike the anatomical methods, PET may allow further assessment of the response rate during chemotherapy. Not much is known about the value of

PET after chemotherapy as a method for evaluation of response. However, some preliminary studies determining the prognostic value of PET after chemotherapy have been reported with promising results.[28, 29, 30] PET might identify non-responders at an earlier stage and thus prevent over-exposure to non-beneficial chemotherapy and/or local treatment. A disadvantage of many PET studies, however, is the use of relatively small patient groups. In addition, many studies are retrospective and based on a select group of patients. A prospective study in a large group needs to be carried out to determine the actual value of PET in these patients. At present, an ongoing multicentre prospective study on the value of PET in this setting is being performed in our hospital.[27]

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Netherlands
The Journal of Medicine

BRIEF REPORT

Pneumatosis cystoides intestinalis, four cases of a rare disease

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ABSTRACT

Pneumatosis cystoides intestinalis (PCI) is a disease in which small gas-filled cysts appear in the intestinal wall. Four cases presented here demonstrate the diversity of the associated diseases. In two of the patients constipation probably played a role; in the third patient decreased colonic motility, elevated intestinal pressure and increased mucosal permeability in the context of enteritis treated with codeine was the underlying problem; in the fourth high protein feeding and bowel ischaemia was diagnosed. Various aetiologies are presented in the literature. There is no specific history and physical or laboratory findings do not help to diagnose PCI. Plain abdominal film, ultrasound, computer tomography, magnetic resonance imaging, barium contrast studies and/or endoscopy may be necessary for diagnosis. Therapy is based on enhancing partial oxygen pressure in the bowel wall. PCI usually runs a benign course.

INTRODUCTION

Pneumatosis cystoides intestinalis (PCI) is characterised by subserosal or submucosal gas-filled cysts in the intestinal tract. After studying 919 cases Jamart found the small intestine to be the most common localisation (42%) followed by the large intestine (36%); in 22% of the cases both small and large intestine were affected.[1] There is still controversy about the exact cause of this condition.[2,3] In the literature it is either associated with a coexisting disease, then called secondary PCI, or it appears without a coexisting condition, called primary PCI. There are associations with inflammatory bowel disease,[4,5] gastrointestinal infections,[6,7] chemotherapy,[8,9] connective tissue disease,[10] systemic lupus erythematosus and many other conditions.[8] There are no typical symptoms or physical signs. The patient may be asymptomatic or have gastrointestinal symptoms varying in severity.[2] We present four cases and discuss aetiologic aspects, clinical presentation, diagnosis and treatment as presented in these cases.

CASE 1

A 56-year-old woman was admitted to the hospital with abdominal discomfort, obstipation and intermittent haematochezia for several days. Physical examination revealed no abnormality except a tender obese abdomen and external haemorrhoids. Routine laboratory examinations, bacterial and parasitic stool examinations and viral serology were negative. Colonoscopy and abdominal CT examination showed multiple submucosal gas-containing 'polyps' and the diagnosis of PCI was made. Treatment consisted of oxygen (10 litres/minute with a mask) for two weeks and a diet suitable for treating the obstipation. The lesions disappeared completely. After one year of follow-up the patient was still without symptoms, and findings at colonoscopy were normal.

CASE 2

A 61-year-old woman was hospitalised because of a swollen and tender abdomen and stools mixed with blood. Her

previous medical history revealed obstipation and PCI five years earlier, treated with intensive (but not hyperbaric) oxygen therapy. Since then she had intermittent complaints of abdominal pain without evidence of PCI. The stool frequency was once every two days. She had also been diagnosed with itching due to xerodermia, polyarthrosis, recurrent bronchitis and transient conjunctivitis in the past five years. Physical examination at admission revealed a tender abdomen, external haemorrhoids and an erythema of the skin on arms and legs. Laboratory evaluation showed a raised erythrocyte sedimentation rate of 58 mm and a positive homogenous antinuclear factor titre of 1/80. Other serological markers for autoimmunity and viral serology were normal, as was stool examination for bacteria and parasites. Skin biopsies showed no vasculitis. PCI was diagnosed by means of sigmoidoscopy and abdominal CT. She was treated successfully with intensive oxygen therapy again.

CASE 3

A 35-year-old man was seen in the emergency department because of watery stools at a frequency of 20 times daily for the last two days. The diarrhoea was preceded by colicky abdominal pain. There was no blood loss. He had been on treatment with ofloxacin and codeine for one day. On physical examination he looked ill with signs of dehydration. There was no fever. Blood pressure was normal. There was loud peristalsis and a tenderness of the abdomen in the right lower quadrant. Rectal examination was normal except for some watery light yellow stool. Laboratory investigations revealed C-reactive protein levels of ten times the normal level and slightly elevated transaminases. Abdominal X-ray showed an oedematous bowel wall of the right colon with intramural air diagnosed as PCI. Treatment was started with intravenous fluid and the quinolones were continued. After 24 hours his condition improved markedly. At that time the patient refused further investigations and he was discharged at his own request.

CASE 4

A 44-year-old man was admitted to the gastroenterology ward because of severe weight loss. Due to recurrent abdominal pain he was unable to ingest sufficient calories to maintain a stable weight. He had a past history of alcoholic pancreatitis and painful pseudocysts necessitating several operations, finally resulting in a subtotal pancreatic resection with jejunal-pancreatic anastomosis. He subsequently developed diabetes mellitus. Recently he presented with an acute abdomen and the subsequent operation resulted in resection of two metres of small intestine. Pathological examination of the resected bowel revealed ischaemia probably due to strangulation caused by adhesions. During his stay he was fed with an artificial diet through a feeding tube positioned in the jejunum. He suddenly developed a diffuse pain in the abdomen with watery diarrhoea. PCI was diagnosed by plain abdominal X-ray and CT scanning. Stool cultures were negative. He was treated with intensive oxygen therapy (10 litres/min with a mask). The submucosal air disappeared in the ensuing days but the pain remained diffusely in the abdomen. An explorative laparotomy was therefor performed. There were multiple adhesions, and a small part of ischaemic small bowel was resected. After this the patient recovered slowly. Finally he was transferred to a hospital near his home with continuous parenteral feeding, which was continued at home after discharge from the hospital.

DISCUSSION

PCI is a rare disease with an acute or subacute clinical presentation. In the literature there is little information about the incidence. Jamart found in his analysis of 919 patients a peak incidence between 41 and 50 years.[1] Man-to-woman ratio was 3:1. The exact origin of PCI is debated. Many theories have been advocated. The most admissible ones are discussed here. First, there is the mechanical theory. It suggests that gas under pressure is forced into the bowel wall through a mucosal defect. It is probably involved in PCI associated with trauma, surgery, endoscopy and in cases that involve bowel obstruction. However, it does not explain the high content of hydrogen present in the cysts.[3] Second, there is the bacterial theory. In animal experiments, introduction of bacteria into the bowel wall by injection has been shown to cause PCI.[11] In these cases the gas in the cysts contained elevated levels of hydrogen. The pulmonary theory has been criticised: the assumption that gas travels from ruptured alveoli through the mediastinum into retroperitoneal space and finds its way along perivascular spaces through the mesentery into the bowel wall could not be proven convincingly.[3] The mucosal damage theory, which states that PCI is preceded by mucosal injury, does not entirely explain the high hydrogen level of the cysts. The exact cause is probably a combination of associated diseases causing elevated pressure and mucosal damage allowing gas-forming microorganisms to enter the bowel wall, thus forming the cysts.

There are no specific anamnestic, clinical or laboratory clues to help to establish the diagnosis as illustrated in the presented cases. Patients can be asymptomatic, or present with abdominal discomfort and rectal blood loss.[2]

In two thirds of the patients a plain abdominal film shows characteristic changes in the intestinal wall (*figure 1*).[1] Additional investigations such as ultrasound, computer tomography (*figure 2*), magnetic resonance imaging, endoscopy or barium contrast studies usually confirm the diagnosis. The first three investigations all show a thickened bowel wall containing gas. Endoscopy reveals submucosal cysts appearing like small polyps with a white or haemorrhagic colour, which collapse on biopsy.

Treatment with oxygen or hyperbaric oxygen is effective.[12,13] It is based on increasing the partial oxygen pressure in the blood and thus increasing the pressure gradient of the gas in the cysts (mainly H_2, N_2, CO_2, methane, ethane and argon) to the dissolved gases in the blood. The cysts become filled with oxygen, which is subsequently metabolised, after which the cysts diminish and finally disappear. Optimal oxygen therapy consists of oxygen through a venturi mask resulting in a PaO_2 of approximately 250 mmHg. It should be continued until at least two days after resolution of PCI to avoid recurrence.[3] Relapse after several years is possible and can be treated successfully. Hyperbaric oxygen (2.5 atmospheric pressure) 1.5-2 hours a day could be used to reduce the duration of oxygen administration and the potential risk of oxygen toxicity to the lung.[13] For practical reasons hyperbaric oxygen is seldom applied. If there is an obvious cause or associated disease, this should be treated. It is important to consider this disease in the context of acute and subacute abdominal symptoms as it sometimes presents as a pneumoperitoneum due to ruptured cysts. Surgery should be avoided unless there are signs of severe inflammation, metabolic acidosis or portal venous gas, which are indicators of more serious diseases. The differential diagnosis then consists of bowel ischaemia or bowel perforation. Portal venous gas is commonly seen with bowel infarction and is an ominous sign related to high mortality.[14]
The explanations for PCI in the presented patients are: elevated intestinal pressure because of obstipation (case 1 and 2), diminished colonic motility by codeine treatment for an intestinal infection in which elevated mucosal permeability, gas formation and elevated intestinal pressure could be the aetiological factors (case 3).
In case 4 the patient was treated with high protein tube feeding because of a short bowel syndrome. Bowel ischaemia was diagnosed at the anastomosis as the cause of PCI.

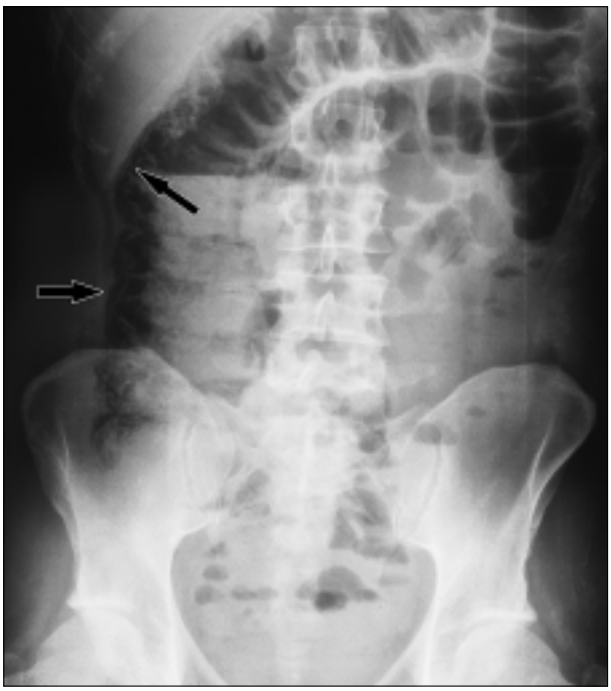

Figure 1
Plain abdominal film showing gas in the colonic wall (arrows).

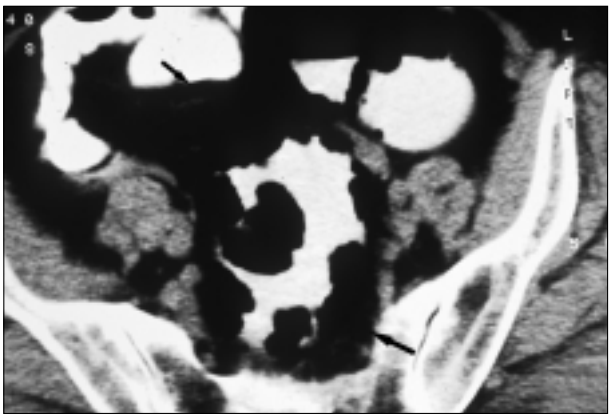

Figure 2
Computer tomography of the lower abdomen showing gas in the intestinal wall (arrows).

CONCLUSION

Pneumatosis cystoides intestinalis is a rare clinical entity, usually benign, in which surgery should be avoided. The treatment is simple and effective with normobaric or hyperbaric oxygen. Further care should be directed at identifying and treating associated diseases and excluding causes such as bowel ischaemia.

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ABOUT THE COVER

Mezzotint 'untitled'

CAROLINE KOENDERS

Caroline Koenders works in Nijmegen. She was trained at the Academy of Fine Arts in Arnhem, the Netherlands. She has participated in a great number of international print-making Biennales (Belgium, Slovenia, Bulgaria, Italy, Sweden, Ukraine), and received scholarships for print-making symposia in Matra Almas (Hungary), Müllheim (Germany) and Salonica (Greece). She has given workshops in the Graphic Studio Engramme in Quebec and in Salonica. She is currently a teacher of graphic arts/print making at the Municipal Centre for Art and Culture in Nijmegen. In addition to a series of individual expositions, she has exhibited her work at many group expositions in the Netherlands and abroad. The Mezzotint (maniere noire) is a speciality of Caroline Koenders. This dry-point technique creates an image originating from a velvet-like dark surface. Light emerges by polishing and scraping this surface.

An edition of this Mezzotint 'untitled' is available. One original print from this limited edition can be ordered at a price of € 200. You can order the print at Galerie Unita, Rijkstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

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BRIEF REPORT

Life-threatening hypokalaemia and quadriparesis in a patient with ureterosigmoidostomy

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ABSTRACT

We report quadriparesis as a result of severe hypokalaemia and acidosis in a 50-year-old man who had undergone ureterosigmoidostomy for bladder extrophy 48 years earlier. Aggressive suppletion with intravenous potassium and bicarbonate combined with potassium-sparing diuretics and ACE inhibitors resulted in complete restoration of the serum potassium and resolution of the neurological symptoms. The underlying mechanism as well as the treatment of hypokalaemia and hyperchloraemic metabolic acidosis after ureterosigmoidostomy are briefly discussed.

INTRODUCTION

Various intestinal segments have been used as conduits to receive urine when the urinary bladder has been removed or is non-functioning. The anastomosis of one or both ureters into the sigmoid (ureterosigmoidostomy) almost always results in hyperchloraemic metabolic acidosis, hypokalaemia and other electrolyte abnormalities (e.g. hypomagnesaemia and hypocalcaemia). Nowadays, this diversion technique is rarely applied because of the high rate of metabolic complications associated with its use. Instead, isolated loops of ileum, jejunum or colon are taken as urine conduits. Since the introduction of the ileal conduit method, the incidence of electrolyte abnormalities has declined considerably.[1]

CASE REPORT

A 50-year-old man was admitted to the hospital for drainage of an abdominal wall abscess that developed 'spontaneously'. He had undergone bilateral ureterosigmoidostomy for bladder extrophy 48 years earlier. He was seen regularly at the outpatient clinic because of mild acidosis and hypokalaemia, for which he received sodium bicarbonate and potassium chloride. His serum potassium was normal (4.0 mmol/l). Following drainage of the abdominal wall abscess, his condition rapidly worsened and he developed generalised muscle weakness. On physical examination, he was alert and afebrile, although he was hyperventilating. The pulse was 72 beats per minute and blood pressure was 130/70 mmHg. There were no pulmonary or cardiac abnormalities. Neurological examination revealed generalised muscle weakness with absence of all deep tendon reflexes. The patient was unable to move his arms or legs or to lift his head from the bed. Fortunately, swallowing and breathing capacity were not disturbed. No abnormal cranial nerve findings or sensory loss were detected. Laboratory investigations revealed severe hypokalaemia (1.9 mmol/l) and severe metabolic acidosis (pH 7.07). The serum bicarbonate was 6 mmol/l, chloride 120 mmol/l, magnesium 0.60 mmol/l, sodium 143 mmol/l, creatinine 324 μmol/l and urea 22.5 mmol/l. The ECG showed hypokalaemic U waves and widening of the QRS complex. Chest X-ray was normal. Ultrasound examination of the upper abdomen showed a dilated collecting system of the right kidney. A diagnosis of hypokalaemic muscle weakness with severe metabolic acidosis causing Kussmaul respiration was made. The patient was treated with intravenous potassium up to 20 mmol/hour combined with bicarbonate, magnesium sulphate and three

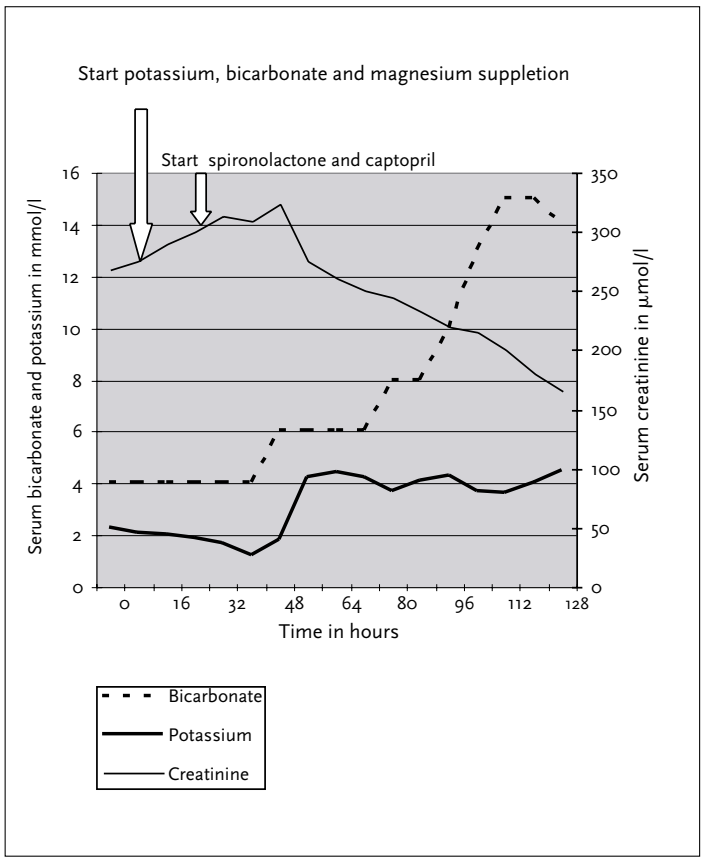

Figure 1

litres 0.9% sodium chloride. Despite this aggressive regime, the serum potassium decreased further to 1.2 mmol/l and the patient developed fever (39 °C). In addition, a combination of potassium-sparing diuretics, ACE inhibitors and antibiotics was administered. This resulted in an increase in the serum potassium to normal values within two days (see *figure 1*). Concomitant with the correction of serum potassium, the neurological symptoms dramatically improved. By then, it became apparent that blood cultures were positive for *Escherichia coli*. Serum bicarbonate normalised approximately four weeks later, as did renal function. Subsequently colonoscopy showed a small polypoid tumour in the right ureteric ostium. The mass was removed by means of snare polypectomy. Microscopical examination revealed adenomatous tissue, but no signs of malignancy.

DISCUSSION

Implantation of the ureters into the gut is commonly used for reconstruction of the urinary tract after extirpative surgery or bladder extrophy. A well-known problem of diversion of urine through intestinal segments is the development of metabolic complications. When the sigmoid is used, severe electrolyte abnormalities such as hyperchloraemic metabolic acidosis and hypokalaemia may occur. Other complications include recurrent infections and osteomalacia.

Chronic *hyperchloraemic metabolic acidosis* secondary to ureterosigmoidostomy was first described by Boyd *et al.*[2] in 1931 in a child who also developed rickets. Since then, numerous investigations have been carried out to elucidate the pathophysiology of this abnormality. Although the mechanism is not completely understood, the acidosis is explained as follows.[3,4] Electrolyte shifts will occur any time urine is in contact with the intestinal mucosa. Urinary ammonia plays a central role in these processes. Ammonium transport is regulated by Na/H antiporters, located at the luminal borders of intestinal cells. The weak acid NH_4 is exchanged for a proton, Na. The exchange of NH_4, however, is coupled with the exchange of serum bicarbonate for luminal chloride. The result is loss of bicarbonate on the one hand and absorption of ammonium chloride in the blood on the other. Furthermore, ammonium transport may also take place through potassium channels. As a result of this metabolic hyperchloraemic acidosis, a net loss of calcium from bones may occur, which can lead to bone demineralisation and kidney stones. Hypocalcaemia may provoke severe complications: tetany in the presence of severe acidosis has been reported in a patient with cloacal extrophy.[5]

Severe *hypokalaemia* is another important metabolic complication. Because urinary concentration of potassium is much higher than the serum concentration, it seems logical to assume that the rectosigmoid would absorb urine potassium, thereby preventing the developement of hypokalaemia. It has been shown, indeed, that the ileum is able to reabsorb potassium. Patients with an ileal conduit do not experience hypokalaemia and have normal potassium body stores.[6] The distal colon, however, is less likely to reabsorb potassium.[7,8] In one third of patients with uretrosigmoidostomy, hypokalaemia and depletion of total body potassium have, in fact, been observed.

The metabolic findings in our patient, however, cannot be fully explained by the passage of urine in the sigmoid. The hypokalaemia was new. Previous laboratory investigations had shown normal serum potassium and only mild acidosis. We suggest that infection and renal obstruction played a major role in this case. Several arguments lend support to this statement. Metabolic acidosis and hypokalaemia in patients with an ureterosigmoidostomy may deteriorate due to renal tubular dysfunction secondary to repeated episodes of pyelonephritis,[9,10] prolonged urine retention in the colon[11,12,13] and hypomagnesaemia.[14] Ascending urinary tract infection is common in patients with uretrosigmoidostomy. Acute pyelonephritis occurs in

10-17% of them and approximately 4% die of sepsis.[15] Hypomagnaesemia, which is often seen in patients with an ureterosigmoidostomy, initiates kaliuresis or causes existing kaliuresis to become worse. Although the pathogenesis is unclear, increased aldosterone activity and impaired distal chloride transport may have played a role, as shown earlier in patients with ileostomy and dehydration.[3] Both aspects, obstruction as well as bacteraemia, were present in our patient. On the one hand there was an *Escherichia coli* septicaemia and hypovolaemia due to an abdominal wall abscess. On the other hand, ultrasound and colonoscopy demonstrated obstruction of the right uretrosigmoidostomy. Taking this into account, it is plausible that infection and tubular dysfunction contributed to the severe hypokalaemia.

As to the therapeutic interventions, some measurements need attention. In stable patients severe deterioration of the electrolyte abnormalities can be avoided by daily administration of oral potassium and bicarbonate, restriction of chloride intake,[16] regular emptying of the colon (nightly insertion of a rectal tube),[17] and timely administration of antibiotics in case of renal infection.
In severely ill patients, as shown here, immediate aggressive suppletion might be life-saving. Bicarbonate and potassium should be administered both orally and intravenously. Correction of the acidosis without potassium replacement might be dangerous, due to progressive paralysis.[3] Hypokalaemia-induced muscle weakness may require mechanical ventilation of a patient.[18] Adequate drainage of the urine is needed in case of ongoing sepsis. In addition, we experienced benefit from treatment with potassium-sparing diuretics and ACE inhibitors. At the time we assumed that the latter treatment reduced the renal excretion of potassium. Afterwards, however, we could not find conclusive literature data on this topic and the exact influence of ACE inhibition remains favourable, but questionable.

Metabolic acidosis occurs far less commonly in patients with an ureteroileostomy, since rapid drainage of urine into the bag means a short contact time, which prevents significant changes in urinary composition.[3, 4, 8] Therefore, we considered constructing an ileal conduit in order to prevent further episodes of hypokalaemia and metabolic acidosis. The patient, however, recovered fully and was unwilling to undergo surgery.

CONCLUSION

We presented a patient with a ureterosigmoidostomy based acidosis and a severe, even life-threatening hypokalaemia developed over a short period of time. Such patients should be promptly treated with a number of (pharmaco) therapeutic measures.

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BRIEF REPORT

Flaccid paresis due to distal renal tubular acidosis preceding systemic lupus erythematosus

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ABSTRACT

We report a 25-year-old woman presenting with a flaccid paresis due to severe hypokalaemia as a consequence of distal renal tubular acidosis (dRTA). Six years after presentation of dRTA, she developed overt symptoms of systemic lupus erythematosus (SLE). dRTA in SLE is often secondary to an interstitial nephritis. In contrast to other reports the dRTA did not resolve after treatment with prednisone in our patient. Nephrocalcinosis might be one of the causal factors in the persistence of dRTA.

INTRODUCTION

Distal renal tubular acidosis (dRTA) is associated with hypercalciuria, exposition to tubulotoxic agents and with several autoimmune diseases such as Sjögren's syndrome and, less commonly, systemic lupus erythematosus (SLE).[1] We report a patient presenting with a flaccid paresis due to hypokalaemia as a consequence of dRTA. Six years after presentation of dRTA, she developed overt symptoms of SLE. Such a long time interval is very rare. Up until now, the longest reported time interval between presentation of dRTA and SLE was four years.[2] Also, in retrospect, dRTA seems to be the first symptom of SLE in our patient.

CASE REPORT

A 25-year-old slender woman presented with an episodic flaccid paresis of the extremities in 1990. On several occasions she was unable to walk, and she dropped cups. These symptoms came and went over a period of approximately one year.

On hospital admission her weight was 45 kg, the blood pressure was 95/60 mmHg and pulse rate 80 beats/min. There was a flaccid paresis of the extremities with intact reflexes. On laboratory examination, the ESR was 60 mm in the first hour, serum potassium 2.0 mmol/l, sodium 141 mmol/l, chloride 118 mmol/l, and creatinine 117 μmol/l. In venous blood the pH was 7.17, PCO_2 5.5 kPa and bicarbonate concentration 14.9 mmol/l. The calculated anion gap (Na^+ - ($HCO3^-$ + Cl^-), normal value 5-11 μmol/l) was 8 mmol/l. Haematological parameters as well as values for serum ASAT and ALAT were within normal limits. Serological tests revealed absent antinuclear antibodies and normal values for complement C3 and C4.

Laboratory analysis of the urine revealed concentrations of sodium of 28 mmol/l, potassium of 27 mmol/l, and chloride of 55 mmol/l. The calculated urinary anion gap (Na^+ + K^+, - Cl^-) for estimating urinary ammonium excretion) was zero mmol/l.[3] The pH of the urine was above 7. After an acid load of 0.1 gram /kg NH_4Cl, the urinary pH decreased from 6.8 to 6.4 (normal <5.3). The maximum urinary calcium excretion was 5 mmol/day during acidosis, but usually below 2 mmol/day (normal value <5 mmol/day). The calculated creatinine clearance was approximately 48 ml/min. There was a slight proteinuria (±0.2 gram/day) and leucocyturia without bacteriuria. Glomerular casts were not seen on light microscopic examination. Extensive work-up for analysis of the raised ESR including urine cultures, CT abdomen, radiographic barium contrast study of the colon and terminal ileum and gynaecological examination revealed no abnormalities.

The presence of nephrolithiasis or nephrocalcinosis was not mentioned in the reports of the radiological examinations.

In conclusion, there was an incompetence of excreting ammonium during acidaemia. A diagnosis of complete dRTA with hypokalaemic paresis was made. No primary cause was found for dRTA, so by definition it was classified as idiopathic dRTA. Besides, there was no explanation for the decreased renal function and the raised ESR. After institution of chronic suppletion of sodium bicarbonate 4 gram/day (±1 mmol/kg/day) and potassium chloride (±0.5 mmol/kg/day) the paresis disappeared.

Between 1990 and 1996 she was admitted to the hospital several times with recurrent symptoms of dRTA which rapidly responded to oral suppletion of sodium bicarbonate and potassium chloride. The main problem seemed compliance with the medication, since she could not tolerate the sodium bicarbonate due to gastrointestinal complaints. An abdominal X-ray taken in 1993 now revealed nephrocalcinosis of both kidneys (*figure 1a*). She passed small stones with her urine on several occasions. She experienced several (ascending) urinary tract infections requiring treatment with antibiotics. The concentration of citrate in the urine was <0.10 mmol/l (normal value 0.5-4.0 mmol/l).

In August 1996 she was readmitted with high fever, arthralgia of both ankles and a butterfly shaped rash on the face after a holiday in Spain. Again she presented with metabolic acidosis and hypokalaemia. There was a thrombocytopenia of 90 x 10^{-9}/l and the complement levels were low: C3: 594 mg/l (normal value: 750-1250 mg/l) and C4: 171 mg/l (normal value: 180-400 mg/l). Serological tests revealed antinuclear antibodies, anti double-stranded DNA antibodies (titre 1:20), and antibodies (ENA) against SS-A. Urinalysis was unchanged with persistent leucocyturia and a slight proteinuria (maximum 0.8 g/l). Glomerular casts were not seen on light microscopic examination. The serum creatinine level was unchanged. The patient refused a renal biopsy. There were no buccal ulcers, no neurological symptoms and there were no enlarged lymph nodes. In conclusion, besides a recurrence of the renal tubular acidosis five ARA criteria were positive, confirming the diagnosis of SLE (butterfly rash, arthralgia, thrombocytopenia, positive ANA and double-stranded DNA antibodies).[4]
Because of severe constitutional symptoms a trial of prednisone 30 mg was started. There was a remarkable improvement of her clinical condition. Although the metabolic acidosis initially seemed to improve after starting prednisone, it recurred (*figure 2*). After tapering the prednisone dose to zero the constitutional symptoms returned, and it was decided to restart the prednisone at 10 mg a day. An X-ray of the abdomen taken in 2000 showed an increase in the *nephrocalcinosis* (*figure 1b*). The creatinine clearance decreased only slightly from ±48 ml/min in 1990 to ±44 ml/min in 2000. Bone mineral density, as measured by dual energy X-ray absorptiometry, performed after one year of steroids, revealed osteopenia of the spine and severe osteoporosis of the right hip. Unfortunately, she broke her hip after a minor accident after four years of treatment with prednisone at the age of 35.

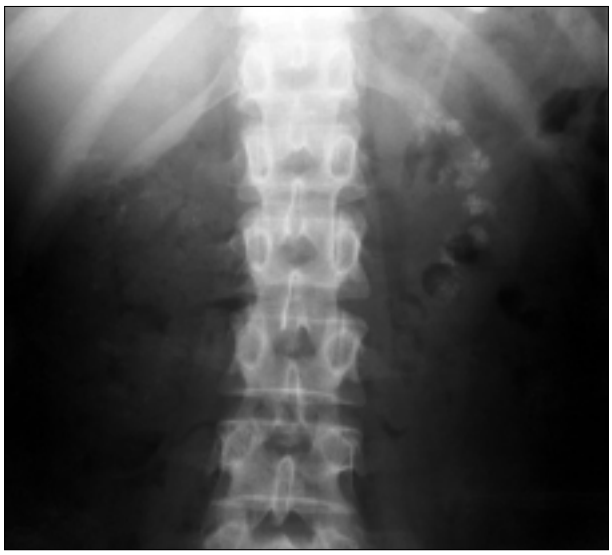

Figure 1a

X-ray of the abdomen taken in 1993, showing severe bilateral nephrocalcinosis three years after diagnosis of distal renal tubular acidosis.

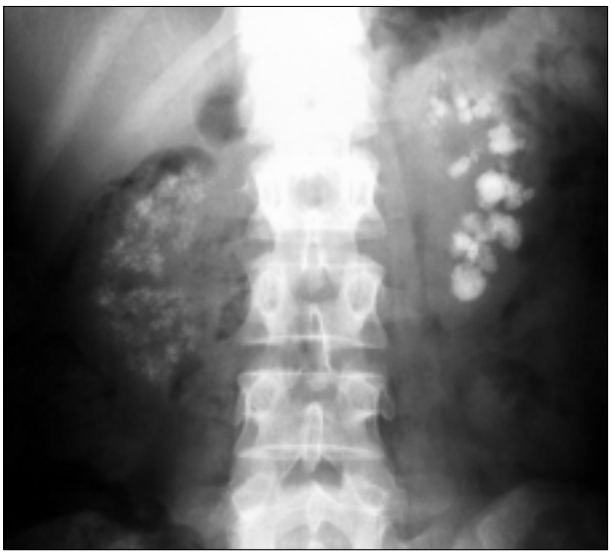

Figure 1b

An X-ray taken in 2000 showed an impressive increase of the nephrocalcinosis.

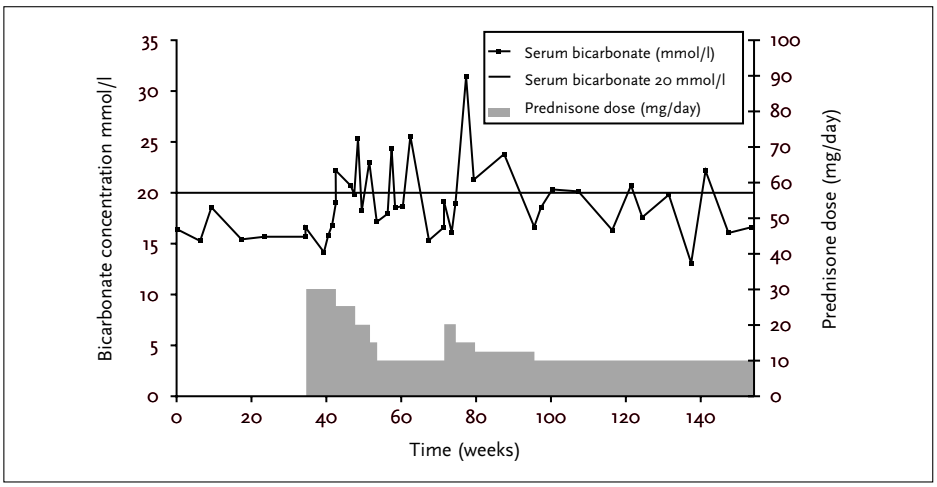

Figure 2

Treatment with prednisone did not cure distal renal tubular acidosis in our patient. Although the serum concentration of bicarbonate seemed to normalise after starting prednisone, it remained low later on.

DISCUSSION

We have presented a patient with a flaccid paresis due to severe hypokalaemia as a consequence of a complete dRTA. Frequently dRTA is associated with hypercalciuria and subsequent nephrocalcinosis, but is also well described in autoimmune diseases such as Sjögren's and SLE.[1] In our patient there was no hypercalciuria when acidosis was corrected and nephrocalcinosis (and nephrolithiasis) became clinically apparent several years after the diagnosis of dRTA. So both hypercalciuria and nephrocalcinosis have to be considered as a consequence and not a cause of dRTA in our patient. As long as six years after the diagnosis of dRTA, other symptoms of SLE became apparent. In retrospect, it is tempting to suggest that hypokalaemic dRTA was the first symptom of SLE in our patient. The unexplained raised ESR at presentation is compatible with this suggestion.

In the literature dRTA has been extensively reviewed.[5, 6] It is characterised by a hyperchloraemic metabolic acidosis accompanied by a reduced renal net acid excretion and the inability to lower the pH of the urine under 5.5 during acidaemia. The defect in ammonium and titratable acid excretion impairs the acidification of the urine and results in acidaemia. The decreased ammonium excretion as calculated with a zero urinary anion gap in our patient during acidaemia as well as the diminished lowering of the pH after an acid load is compatible with this type of dRTA. In contrast to dRTA, in proximal renal tubular acidosis the ability of acidification of the urine is maintained. So, in the latter condition, the urinary anion gap is negative during acidaemia and the urinary pH decreases after an acid load in these patients. Proximal renal tubular acidosis is characterised by a reduced reabsorption of bicarbonate in the proximal tubules. Patients with dRTA often have hypokalaemia as a result of excessive urinary excretion of potassium, but also hyperkalaemic variants occur.[7, 8] Muscle weakness is a well-known symptom of hypokalaemia, and several patients with severe hypokalaemia complicated by paresis and even respiratory arrest have been described.[2, 9] Many patients with hypokalaemic dRTA have hypercalciuria and hyperphosphaturia as a consequence of the buffering of chronic acidaemia by bones and many such patients develop nephrocalcinosis.[10] Calcium phosphate precipitation in the kidney is promoted by a high urinary pH and hypocitraturia.[11] Chronic acidaemia decreases the renal excretion of citrate.

SLE is associated with a variety of tubular defects. When tested in patients with acute exacerbations of SLE, 60% have a distal tubular acidification defect.[12] Approximately 2-30% of patients with SLE have a complete, although often asymptomatic, dRTA with systemic acidaemia.[8, 12] It has been suggested that these patients have an overlap-syndrome of Sjögren's syndrome and SLE, since some patients (like our patient) have antibodies against ENA-SS.[8] Our patient however, did not have clinical signs of Sjögren's syndrome.

Renal biopsy of patients with dRTA and SLE generally shows interstitial nephritis although a correlation between tubular (dys)function and the degree of histological interstitial lesions is usually absent.[12, 13] The persistent leucocyturia and the slight proteinuria without glomerular casts in our patient are fitting with the diagnosis of isolated interstitial nephritis. However, histological proof is lacking, and also nephrocalcinosis can be associated with proteinuria.[14] In our opinion a renal biopsy is indicated for guidance of the immunosuppressive therapy in such patients, especially in case of renal failure or significant proteinuria, where concomitant glomerulonephritis requires more intensive immunosuppression. Immunohistochemical studies in patients with hypokalaemic dRTA and SLE have not been performed yet, but in patients with hypokalaemic dRTA and Sjögren's syndrome an absence of H^+-ATPase in the intercalated cells in the distal tubules has been demonstrated.[15] The absence of H^+-ATPase restrains

excretion of H^+ and thus impairs the formation of urinary ammonium and the excretion of ammonium with the urine. Whether the absence of H^+-ATPase is the result of a generalised dysfunction of the intercalated cells or of a specific immunological destruction of H^+-ATPase is not known.

Adequate treatment of the primary cause of dRTA (withdrawal of the toxic agent) potentially cures dRTA. A causal treatment of the primary cause is not always possible and the interstitium might become irreversibly damaged due to the primary cause or due to long-standing dRTA (nephrocalcinosis). Therefore, symptomatic correction of the chronic acidaemia is the mainstay of treatment in such cases of dRTA. Restoring the acidaemia with sodium bicarbonate (±1-2 mmol/kg) and especially (potassium) citrate is known to prevent nephrocalcinosis, urolithiasis and probably also osteoporosis.[16] Hypokalaemia in dRTA is also corrected by restoring acidaemia, sometimes potassium suppletion is not even necessary. Suppletion of potassium without correction of the acidosis leads to recurrent hypokalaemia as a result of ongoing urinary potassium wasting.[7] The inability of the distal tubular cells to establish a steep lumen/peritubular H^+ gradient reduces the rate of H^+/Na^+ exchange. Consequently, more potassium is secreted in exchange of sodium to maintain intraluminal electroneutrality.

In patients with SLE and Sjögren's syndrome treatment of the interstitial nephritis with steroids can restore renal tubular acidosis.[2, 17] In our patient treatment with steroids only had a marginal effect on the acidosis, while the serum bicarbonate remained low (*figure 2*). Of course, this resistance of dRTA to treatment with glucocorticoids might be due to a diffuse and irreversible destruction of the tubular interstitium. The resistance of dRTA to glucocorticoids in our patient therefore required (aggressive) symptomatic treatment with alkali therapy to prevent complications of dRTA. Unfortunately, neither sodium bicarbonate nor potassium citrate were tolerated by our patient, leading to all the known complications related to untreated dRTA. The slow deterioration of the renal function is presumably due to recurrent ascending urinary tract infections related to the extended nephrocalcinosis and nephrolithiasis, in combination to chronic interstitial nephritis.

In conclusion, distal renal tubular acidosis can be the first manifestation of SLE preceding other symptoms of SLE by years. dRTA in SLE is usually the result of interstitial nephritis. In contrast to earlier reports the dRTA in our patient did not respond to treatment with prednisone. This may be the result of long-standing interstitial nephritis as well as of concomitant nephrocalcinosis. Therefore, symptomatic correction of the chronic acidaemia with alkali therapy was required. Unfortunately, our patient did not tolerate alkali therapy. The persistent dRTA led to recurrent symptomatic hypokalaemia, progressive nephrocalcinosis, frequent urolithiasis, renal insufficiency and in combination with the long-term use of glucocorticoids to an osteoporotic fracture.

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Netherlands
The Journal of Medicine

Selection for the internal medicine residency programme in the Leiden region

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ABSTRACT

Background: The selection and the professional training for a resident in internal medicine requires a great investment of time, training effort and money. Drop-outs are therefore considered a failure of the selection procedure. To evaluate our selection model and outcome of the training programme, we determined the drop-out rate at the Leiden University Medical Centre with its affiliated hospitals.

Methods: Data were collected from all files that have been kept from 1988 onwards of all internists trained and registered in Leiden. These files contained the application forms, the assessments of the trainers and references and the specifications of the programme. Also the first employment as board-certified internist is registered.

Results: The drop-out percentage of the training programme was 8.5%. The drop-outs did not differ in study characteristics from those who successfully completed the programme. The reports from the training team members showed that the drop-outs were as suitable and motivated as the other candidates. During the training programme 8.5% of the residents moved to another university to complete their training as an internist. All board-certified internists who graduated at the Leiden University Medical Centre found a job.

Conclusions: The efficacy of the selection procedure for trainee internists is more than 90%. There are no studies in the literature for a comparison of data.

INTRODUCTION

In the Netherlands, the professional training of internal medicine specialists is conducted at eight university medical centres with their affiliated hospitals. This six-year programme is characterised by continuous learning moments provided and supervised by individual internists in the teaching hospitals ('master-apprentice relationship'). In addition, there is regular joint programme-oriented consultation and teaching (consultation with pathologists, radiologists, and surgeons, discussions of patients, referral meetings, and short courses). Training almost always takes place in two institutions, namely a university and a non-university teaching hospital. While under training, the future internist is supervised by a succession of specialist teachers. This requires great effort, on the part of both the trainee and the teachers. Prematurely breaking off the training means a great loss of invested time, money, and training effort for both parties, not to mention the personal disappointment. It is therefore of the utmost importance during the selection procedure to make as accurate an assessment as possible of whether candidates are suitable for the profession and will be able to complete their training programme and subsequently have successful careers as internists.

In the evaluation of the selection model in the Leiden region, information on newly qualified internists who completed the training programme and those who failed to do so has been studied. Investigations also focused on whether (un)successful completion could be predicted on the basis of facts that emerged during the selection period. A number of specifications of the programme and of the candidates were also studied.

MATERIALS AND METHODS

Selection procedure in the Leiden region

In the Leiden region, applicants interested in a residency must register centrally with a letter of application and a completed standard application form. Selection rounds are held every six months. The first selection is conducted by the regional programme director, who is also the chairman of the regional training committee. This person decides who is to be invited for an interview (first round). The references provided by all these candidates are then collected for information. All those selected have successive individual interviews (all on one day) with five professors of the university teaching hospital (second round). The members of this training team grade each candidate and submit written reports to the programme director. In a joint meeting, the most suitable candidates are selected. These candidates are given the opportunity to indicate their order of preference for the six regional non-university teaching hospitals where they would like to follow the non-academic part of their training (2-4 years). Usually, an interview takes place with the training team of the first two teaching hospitals selected by the candidate (third round). These regional training teams indicate which candidates they would want to admit to their training programme and whom they would prefer not to accept. After the information from the interviews held in the university hospital and in the non-university teaching hospitals is matched, a choice is made by the regional programme director, taking into account the results of the applications, the available places, and the preferences of the candidates. A preliminary training programme is determined and submitted to the Medical Specialists Registration Commission for approval.

Programme specifications and outflow study

Since 1988, files have been kept of all internists trained and registered in Leiden, containing the original application forms, assessments by trainers and references, and the specifications of the programme. Information on where the internist has continued his or her career after registration is systematically stored. The current place of employment is usually also known. This part of the study covers all 102 qualified internists from the Leiden region who registered as internists between 1 January 1988 and 31 December 2000.

Drop-out study

Since 1989, files have been kept of every successive accepted candidate, containing the application forms, the assessments by trainers and references, and the specifications of the programme. The present study covers all 59 persons who, between 1 January 1989 and 31 December 1994, began their training as internists. The success rate of this group is 100% because all residents in this group of research subjects registered as internal medicine specialists before 31 December 2000.

RESULTS

Programme specifications and outflow study

The programme specifications are listed in *tables 1* and *2*. Men continue to constitute the larger part of the group of residents. The average duration of the programme is five and a half years and ranges from four to eight years. Programmes were shorter for persons who served as non-trainee residents, who conducted academic research or who left prematurely to subspecialise, and extended for

Table 1
Trainee and programme characteristics

Men : women*	73 : 29 (72% vs. 28%)
Mean age (range) at MD degree	27 years (24-36)
Mean waiting period (range)	2.0 years (0.04-11)
Mean age at start specialist training programme (range)	29 years (24-37)
Mean age at becoming a board-certified internist (range)	34 years (30-42)
Mean duration of the specialist training programme (range)	5.5 years (4.0-8.0)

** there were no differences between men and women for the other variables*

Table 2
Profile specifications of residents at admission

Cum laude graduation	
Yes	22%
No	50%
Unknown	28%

Medical school at Leiden University	
Yes	61%
No	39%

Administrative functions during medical school	
Yes	85%
No	15%

Voluntary student researcher	
Yes	75%
No	25%

PhD study before or during residency	
Yes	23%
No	77%

those who combined the training programme with PhD research. The average two-year waiting period between the final medical examinations and the start of the specialist programme is usually filled with work as a non-trainee resident, (academic) research, military service, or a combination of these. A quarter of the researchers had started with their PhD research before the start of the specialist programme. This group obtained a PhD before registration as an internist.
A *cum laude* graduation from medical school is considered an asset when applying for access to the residency programme. A pass with distinction could only be established for 22% of the residents. At least half of the researchers did not have this designation. It is remarkable that a considerable percentage of the candidates (39%) did not study medicine in Leiden. On the contrary, many students from other universities enrolled in the Leiden specialist programme. Amsterdam, Rotterdam, Utrecht, Nijmegen, Groningen, and universities abroad provided 13, 10, 3, 6, 6, and 2%, respectively, of the residents.
Most trainee internists performed some research on a voluntary basis when they were medical students or held administrative functions, usually in student associations. It is impossible to say whether the profile as depicted in *table 2* leads to a greater chance of entering the specialist training programme since this information is lacking for the large group of candidates who were not accepted.

Table 3
Outflow characteristics immediately following registration (n=102)

Subspecialising and PhD research	43% (LUMC*) + 5% (non-LUMC)
Subspecialising without PhD research	29% (LUMC) + 5% (non-LUMC)
Staff member internal medicine with or without PhD research	10%
Internist in hospital abroad	4%
Internist in non-university hospital	3%
Pharmaceutical industry	1%

* *LUMC = Leiden University Medical Centre*

Table 4
Current positions held at December 2000 (n=102)

Subspecialising and PhD research	23%
Subspecialising without PhD research	4%
Member of staff in university hospital	28%
Internist in non-university hospital	36%
Internist abroad	5%
Pharmaceutical industry	1%
Unknown	3%

Twelve of the 29 female residents (41%) had a total of 13 pregnancies. The pregnancies took place almost exclusively in the last (academic) part of the programme.
Table 3 presents information on the period following qualification as an internist. The majority of the newly qualified specialists expanded their careers by subspecialising, sometimes in combination with PhD research. Only 7% left immediately for a peripheral hospital in the Netherlands or abroad.
As concerns the subspecialties, most trainee internists went on to nephrology (23%), haematology (20%), or gastroenterology (15%). A smaller percentage opted for intensive care (12%), infectious diseases (11%), oncology or endocrinology (both 7%) for the endorsement. Finally, a further 5% subspecialised in rheumatology. The chosen subspecialty coincided with the preference as expressed on the original application form or in the letters of the members of the training team, in only a minority of cases (27%).
Table 4 gives an overview of the current functions of the 102 internists from the 1988-2000 cohort. It shows that, by now, one third have found a permanent staff position and that most candidates ultimately go to a peripheral hospital. Of the 102 candidates, 47 have obtained their PhD and approximately 23 are still working on their dissertation. Five internists from this cohort have become professors.

Drop-out study
Of the 59 persons who started the programme in the period between 1989 and 1994, five (four men and one woman) prematurely ended their training (8.5%). Two of these never started the programme. The other three were in training for three months, one year, and three years, respectively. The drop-out occurred in different hospitals, the current speciality is known for four of them: radiologist, pathologist, rheumatologist, and head of a blood transfusion laboratory. Reports from the training team gave no indications that these candidates would stop. The drop-outs were as suitable and motivated as the other candidates. However, the drop-outs were on average older when they started or should have started the programme (they were 28, 30, 32, 33, and 39 years of age), and two (i.e. 40%) already had a PhD as against 23% of the non-drop-outs. There were no other clear distinctions in the profile (*table 2*).
In the period under review, another five (8.5%) residents exchanged the Leiden area for a different training region. One trainee came to Leiden from another Dutch training region.

DISCUSSION

Our evaluation study into the effectiveness of the selection procedure for internists shows that more than 90%

of the accepted candidates successfully completed the programme and subsequently found a job. Two of the five drop-outs cancelled before the actual start of the programme. The other three were in training for an average 18 months. The loss of invested labour-intensive teaching effort therefore ultimately concerns three of the 59 candidates (5%). In the literature, no previous publications on non-completion of internist training programmes were found, so comparison with other internal medicine training programmes is not possible. However, there is an article by Keeman and Lagaay on the selection of trainee surgeons from which a drop-out percentage can be calculated.[1] Keeman and Lagaay assessed the 1984-1987 cohort in 1988. This cohort consisted of first-year to fourth-year trainee surgeons. Two of the 63 residents (3%) had dropped out. Unfortunately, no drop-out percentage is known after a complete follow-up assessment of the cohort. Two other residents were considered to be unsuitable and were transferred to a different hospital. What happened to these two candidates is not known either. The Medical Specialist Registration Commission in the Netherlands does not have data on drop-outs from specialist training programmes (...personal communication).

On average, the five drop-outs in our study were older, and a larger percentage of them had a PhD at the time they started the programme, compared with the non-drop-outs. Given the fact that the number of individuals involved is very small, no conclusions can be drawn.
It cannot be determined whether aspects of the profile (*table 2*) and other factors that are not mentioned will increase a candidate's chances to be admitted to the specialist programme, because no data are available on the candidates who were not selected. It can be generally stated that a non-required letter of recommendation, (academic) on-the-job training abroad, arranged by the candidate him/herself, evidence of own initiative, both as concerns the study and otherwise, or excellent study results will impress the selection committee favourably. An excellent assessment of the candidate's period as a non-trainee resident at one of the non-university teaching hospitals will increase the chance of a residency. A satisfactory non-trainee residency in the Leiden University Medical Centre is almost always followed by enrolment in the programme.
In the course of the programme, 8 to 9% of the residents left Leiden to continue their training in another region. For the Leiden region, this means that an experienced resident leaves and a new, inexperienced resident, who needs more intense supervision, enters the programme. In other words, the profit of the teaching investment is cashed in another regional training programme. Nationally, and also from the perspective of the resident, there is no loss of teaching effort. A change of region is probably experienced as an enrichment by the resident.

The outflow study shows that only a few of the newly qualified specialists left directly for a peripheral hospital. A total of 92% continued their careers in an academic environment, 10% of them outside the Leiden region. At least two factors affect this tendency. The first is the restrictive attitude of the training team in admitting candidates who already have a PhD, since they show a greater tendency, after registration, to leave for the non-university hospitals. Since the majority of the candidates do not take their PhD until after their registration, usually in combination with completing their subspeciality, a sort of nursery is thus created for internal medicine scientific work and staff recruitment. The other important factor is the demand of the non-university hospitals for colleagues with a subspeciality. With an eye to the future, the expected shortage of internists may lead to a reduced demand for subspecialities and the PhD research projects linked to these programmes. In our view, this tendency will affect the recruitment for academic staff functions. In combination with the expected shortage of medical school graduates (i.e. an evaporating reservoir of potential temporary researchers), this tendency may lead to less scientific output.
As far as is known, none of the participants in this study are unemployed (*table 4*). However, we want to emphasise that no information was available as to whether the participants found jobs, which were their first choice. Also, information about the length of the application periods for these jobs was not registered. Furthermore, information on whether the jobs were fulltime and information on job satisfaction is lacking.

Finally, we would like to state that our descriptive study on material collected in the past cannot lead to firm conclusions, mainly because a control group is missing and the available information was not comprehensive enough for more detailed research questions. However, given the relevance of the subject for both society and the training teams, we forwarded these results in order to stimulate a discussion on the 'ideal selection procedure' and to argue for more (combined) research on this issue.

Acknowledgments
We want to thank Dr. K.J. Heering, Dr. J.C.M. van der Vijver, Dr. E.J. Buurke, Dr. F.H.M. Cluitmans, Dr. R. Bieger, Dr. J.W. van 't Wout, Dr. R.M. Valentijn, Prof. R. van Furth, Prof. L.A. van Es, Prof. R. Willemze and Prof. F.J. Cleton for their conscientious selection of the candidates.

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[2.] Kaplan NM. Clinical Hypertension. 7th Edition. Baltimore: Williams & Wilkins; 1998.

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