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PHOTO QUIZ: An adult with lower abdominal pain, see page 495

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The *Netherlands Journal of Medicine*: seven years editorial office in Nijmegen, entering a new era

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This December issue of the *Netherlands Journal of Medicine* ends the special 50th anniversary year in which we gave former editors in chief the opportunity to describe the history of the journal from its birth, backgrounds and development to its present shape.[1-5] In my opinion, this series of reports has become a valuable personal account of the great efforts, large personal input and difficulties in publishing an international scientific medical journal of high quality in the Netherlands, and reflects the enormous changes that took place during these years from the transition from handling hand-typed manuscripts sent by ordinary mail to the modern electronic era in a different world. It is now my turn as the current editor in chief to give a report of the last four Nijmegen years (2005-2008). The former editor in chief, Jos van der Meer, has already described the reshaping of the journal, starting from scratch because of the change in publisher, after we took over the editorship from our colleagues in Utrecht in January 2002.[5] After Jos van der Meer resigned as editor in chief and I took over, we were lucky to find Joost Drenth willing to join the editorial board as associate editor; he has been crucial in bringing the journal into the modern electronic era.[6] From 2007, Paul Smits was replaced by Jack Wetzels, while Theo Thien and our editorial assistant Geeralien Derksen-Willemsen remained on board during the whole period.[7,8]

One of the key milestones for the *Netherlands Journal of Medicine* was its immediate appearance online on PubMed and obtaining the status of 'Open Access' journal in 2005. In addition, we implemented an online submission and reviewing system (Manuscript Central) in February 2006. This has led to a substantial increase in submissions, especially from abroad, to around 300 in 2007 (*figure 1*). The rejection rate has increased considerably to more than 50%, and we have become much more selective in accepting papers. More efficient handling of submissions shortened the reviewing time from submission to final decision to an average of 38 days in 2007. Our greatest achievement has been to break the impact factor barrier of 1 in 2007. It was with great pride that we were able to announce an impact factor of 1.548 in July 2007 (*figure 2*), accompanied by the fact that the journal was moving up fast in the ranking of regional general medical journals. To reach that goal we do, of course, depend on the input from our contributors. In *table 1*, the ten best-cited articles during the Nijmegen editorship over a period of seven years are presented.

To provide insight into the background of the articles that we published during the entire Nijmegen editorial period, details are presented in *figure 3*. Between 2002 and September 2008 we published 774 papers that were written by a collective of 1916 authors (2.47 authors per article). Nine Dutch scientists published more than ten articles each in the journal and were responsible for 129

Figure 1. *Number of submissions to the Netherlands Journal of Medicine during the Nijmegen editorial board period*

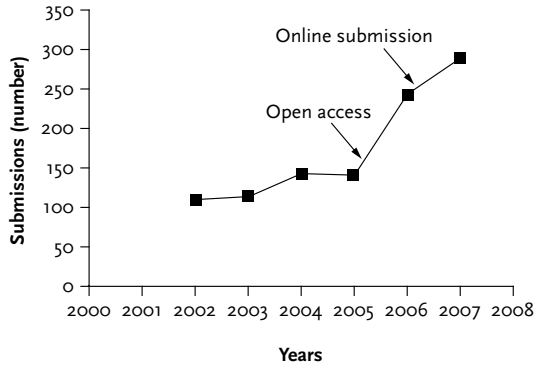
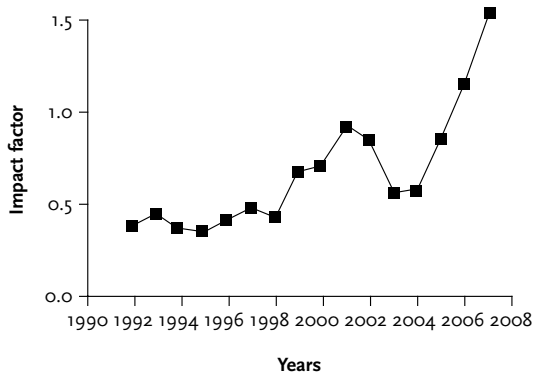


Figure 2. *Impact factor of the Netherlands Journal of Medicine over the years, reaching 1.548 in 2007*

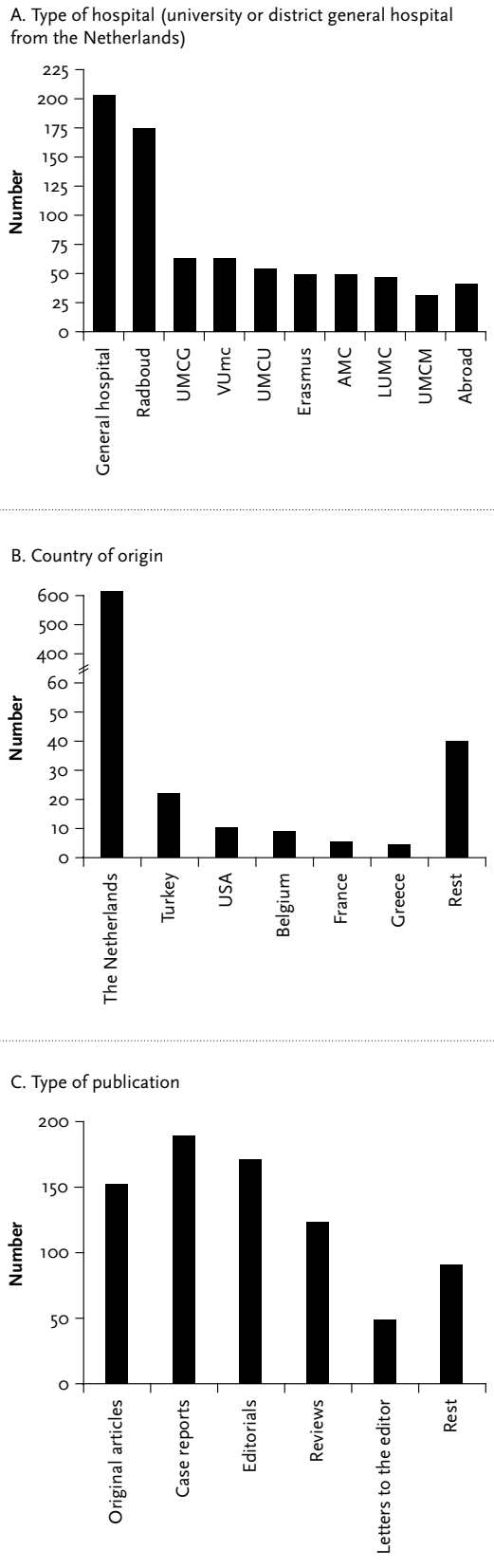


manuscripts. The large majority of the published papers (68%) originated from the Dutch university medical centres. Physicians from 30 different district general hospitals from the Netherlands contributed 26% of the papers published in the journal (*figure 3A*). Authors from 32 countries submitted articles to the journal. As to be expected, the large majority of publications (80%) were of Dutch origin, but we received many submissions from Turkey, USA and Belgium (*figure 3B*).

Figure 3B shows the subdivision in the types of publications. We published 171 editorials and special reports during the Nijmegen years. Although it was sometimes difficult to fill these pages, we found this part of the editorial job very satisfying, as it made the journal more lively and attractive. Remarkable is the increase in the number of letters (both national and international) that we have witnessed over the years, indicating that the journal is viable and well read in a large number of other countries, no doubt due to the open access format.

Looking back at the last years of the editorial office in Nijmegen, I think it is fair to state that we as editors have collectively set in place the requirements for a professional journal, which should provide an opportunity to grow even further. On the other hand, there are also a number of threats which could hinder further improvement and need to be resolved: the number of good original papers and reviews that are submitted is still far too low, and the appearance of subspeciality journals in Dutch, sponsored by industry, may guide potential good material away from our journal, as pointed out earlier.[5] In addition, it is sometimes rather difficult to find reviewers who are willing to spend enough time and effort in writing critical reports. The further increase in impact of our journal may help us to cope with these problems. The number of submissions as case reports, on the other hand, is relatively large and still increasing, and the rejection rate rose to 75% in

Figure 3. *The number of published articles from the Netherlands Journal of Medicine*



The y-axis denotes the number of articles, while the x-axis describes the various categories.

Table 1. *Ten best cited articles in the Netherlands Journal of Medicine from 2002-2008*

Authors	Title	Publication date	Total citations 2002-2008
Van Venrooij WJ, Hazes JM, Visser H	Anticitrullinated protein/peptide antibody and its role in the diagnosis and prognosis of early rheumatoid arthritis	November 2002	46
Jazet IM, Pijl H, Meinders AE	Adipose tissue as an endocrine organ: impact on insulin resistance	June 2003	31
Bodar EJ, van der Hilst JCH, Drenth JPH, et al.	Effect of etanercept and anakinra on inflammatory attacks in the hyper-IgD syndrome: introducing a vaccination provocation model	July-August 2005	29
Netea MG, Ferwerda G, de Jong DJ, et al.	NOD2 3020insC mutation and the pathogenesis of Crohn's disease: impaired IL-I beta production points to a loss-of-function phenotype	September 2005	23
Bleeker-Rovers CP, Bredie SJH, van der Meer JWM, et al.	F-18-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis	October 2003	22
Van Bommel EFH	Retroperitoneal fibrosis	July 2002	21
Riksen NP, Smits P, Rongen GA	Ischaemic preconditioning: from molecular characterisation to clinical application - part I	November 2004	19
Hommes DW, Oldenburg B, van Bodegraven AA, et al.	Guidelines for treatment with infliximab for Crohn's disease	July-August 2005	17
Arend SM, Breedveld FC, van Dissel JT	TNF-alpha blockade and tuberculosis: better look before you leap	April 2003	17
Klein SK, Slim EJ, de Kruif MD, et al.	Is chronic HIV infection associated with venous thrombotic disease? A systematic review	April 2005	16

2007.[9] In order to improve the standard of the submitted case reports, especially for the young colleagues for whom writing a case report is frequently their first scientific exercise, we have produced detailed guidelines, which we urge prospective authors to take note of.[9,10] Eventually, this should also benefit the journal.

After seven years of editorial board in Nijmegen, it is time for a change. The editorial board is moving to Amsterdam under the leadership of Professor Marcel Levi as of 1 January 2009. I wish him and his team a lot of success, and hope that they will find working for the journal as enjoyable as we have done and that the Amsterdam team will succeed in getting our journal to climb even higher in the ranking.

I thank my colleagues and all our contributors for helping to bring the journal to its present standard!

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EDITORIAL

Blood pressure measurement in the year 2008: revival of oscillometry?

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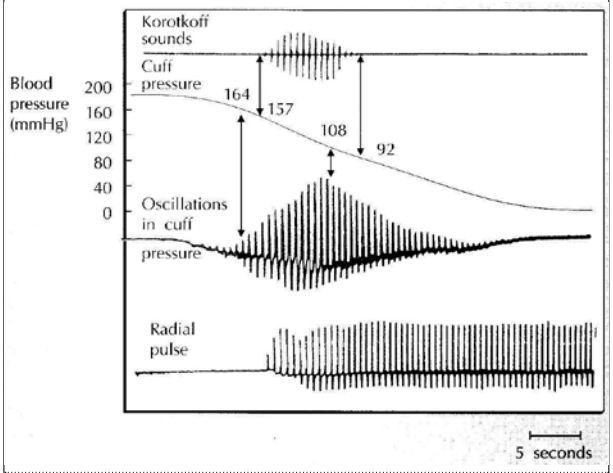
INTRODUCTION

In this issue of the Journal, attention is given to some aspects of blood pressure (BP) measurement by oscillometry.[1] In fact the oscillometric principle is a very old one and some of our elderly colleagues may remember the application in the oscillogram, used when a patient was suspected of having one-sided leg ischaemia. In such cases, oscillations in BP were different between the two legs, i.e. the affected leg showed oscillations with a smaller amplitude. When BP is measured oscillations are visible from suprasystolic to infradiastolic BP, but the oscillations show varying amplitude, as can be seen in *figure 1*, a well-known registration from the work of Geddes' group.[2]

Figure 1. *The oscillations when the pressure in the bladder decreases*



For comparison the blood pressure (BP) measurement according to the Korotkoff sounds is also given. In this model, the diastolic BP can be calculated from the mean arterial pressure (MAP) and the systolic BP, with the classic formula DBP = MAP – (SBP – MAP)/2, thus in the figure DBP = 108 – (164 – 108) /2 = 108 – (56 /2) = 80 mmHg.

HISTORY

In 1876, the French physiologist Marey reported that he had already been using the oscillometric method for 25 years.[3] At the time, the meaning of the maximal amplitude of the oscillations was hotly debated and a number of investigators, but not Marey himself, stated that the maximal amplitude was found at diastolic BP. The question then moved to the background due to the development of the Riva-Rocci/Korotkoff method for indirect BP measurement. In the late 1970s, new interest in oscillometric BP measurement arose mainly from work by anaesthesiologists,[4,5] who were looking for noninvasive methods to monitor BP in postoperative and/or intensive care patients. At that time there was more or less consensus that the oscillations with the maximal amplitude stood for the mean arterial blood pressure (MAP).

Then the aim shifted to deriving a systolic and a diastolic BP from the MAP. The algorithms of the (probably different) methods to calculate the systolic (SBP) and diastolic (DBP) were not disclosed and were sometimes changed without reporting that to users.

In another paper in this same issue of the Journal the Riva-Rocci technique is compared with the Korotkoff technique.[6] The next step may be to study the relation of the calculated SBP, derived from an oscillometric BP reading, with the two 'gold standards', namely the Riva-Rocci and the Korotkoff technique.

MEAN ARTERIAL PRESSURE

What were the advantages of using the MAP? The anaesthesiologists preferred to use one number for the BP when reporting the haemodynamic state of the monitored patient and the second was that with a MAP they could more easily calculate the total peripheral resistance (TPR) to have a

better idea about the balance between vasoconstriction and vasodilatation. But since most doctors and nurses are trained in measuring SBP and DBP and are accustomed to diagnosing and/or treating patients according to the limits for SBP and DBP given in guidelines, the MAP is not familiar enough to physicians, nurses and patients for everyday use. And thus, the situation has arisen that some devices used for self or home measurement that really measure the MAP only give the calculated SBP and DBP in the display with the consequence that sometimes the MAP is 're' calculated from the calculated SBP and DBP, as is also mentioned by Kiers *et al*.[1]

DIFFERENCE BETWEEN MEASURED AND CALCULATED MAP

Because, as stated earlier, the methods for calculating SBP and DBP are not published or revealed to the researchers in the field, it is no surprise that investigators compare the differences between the two MAPs, as has also been done by Kiers *et al*.[1] In our own experience large individual differences exist between calculated and measured MAP, which we illustrate in three hypertensive patients and in one normotensive individual (*tables 1* and *2*). On the other hand, when the number of readings increases, the correlation becomes stronger, although there are still individuals in whom the difference is of clinical importance. In *figure 2* the original (= measured) MAP and the calculated MAP are derived from the 24-hour registration and the correlation is very high, but in the lower panel the exceptional cases are still present.

Table 2. *Two additional examples in a normotensive and a hypertensive patient of the unpredictable relation between the similar measured MAP and the accompanying calculated SBP and DBP and consequently as MAP (c)*

MAP (M)	BP (C)	MAP (C)	M-C
131	167/97	120	11
	187/100	129	2
	178/102	127	4
	162/105	124	9
84	110/69	83	1
	137/58	84	0
	122/67	85	-1
	128/57	81	3

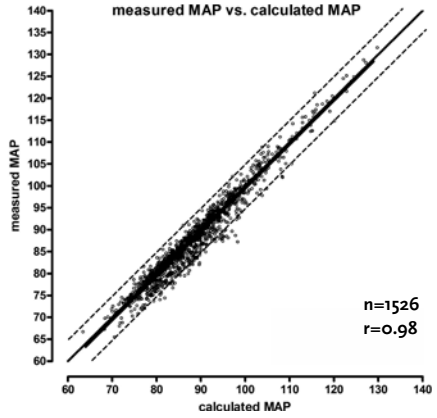
In the normotensive individual both MAPs are almost identical despite a large variation in the SBPs (27 mmHg) and DBPs (12 mmHg).
SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure (SBP - DBP); HR = heart rate.

Table 1. *Two examples of the comparison of the measured (M) and the calculated (C) mean arterial pressure (MAP) within one continuous session of blood pressure measurements of two treated hypertensive patients*

MAP(M)	SBP	DBP	PP	MAP(C)	HR	M-C
Patient 1						
142	186	108	78	134	74	8
137	168	107	61	127	74	10
148	187	106	81	133	72	15
146	178	100	78	126	74	20
132	175	110	65	132	78	0
147	189	111	78	137	78	10
149	177	104	73	128	76	21
123	162	101	61	121	72	2
131	167	97	70	120	73	11
126	173	104	69	127	72	-1
129	159	101	58	120	75	9
Patient 2						
119	220	95	125	137	92	-18
120	182	84	98	117	73	3
105	198	84	114	122	72	-9
128	189	97	92	128	71	0
125	197	89	108	125	68	0
116	183	89	94	120	70	-4
116	195	80	115	118	69	-2
88	182	81	101	115	72	-27
107	195	90	105	124	67	-17

SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure (SBP - DBP); HR = heart rate. C is calculated in the classical manner: MAP = DBP + 1/3 PP.

Figure 2. *The upper panel shows the correlation between original (= measured) and calculated mean arterial pressure (MAP), the lower panel shows a Bland-Altman plot of the same 1526 patients as in the upper panel*



Both MAPs are the means from the 24-hour recordings with about 40 to 80 readings. The unbroken line is x = y, the broken lines are the +5 and -5 mmHg.

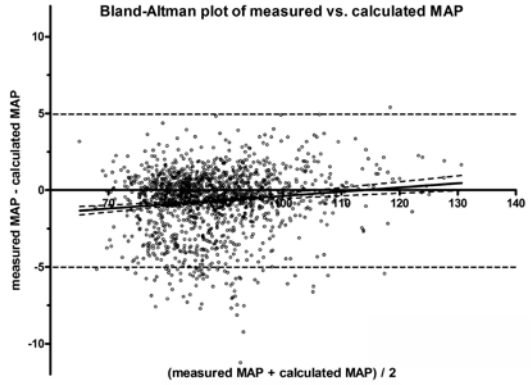


Table 3. *Comparison of the advantages and disadvantages of the three principles for the noninvasive measurement of blood pressure*

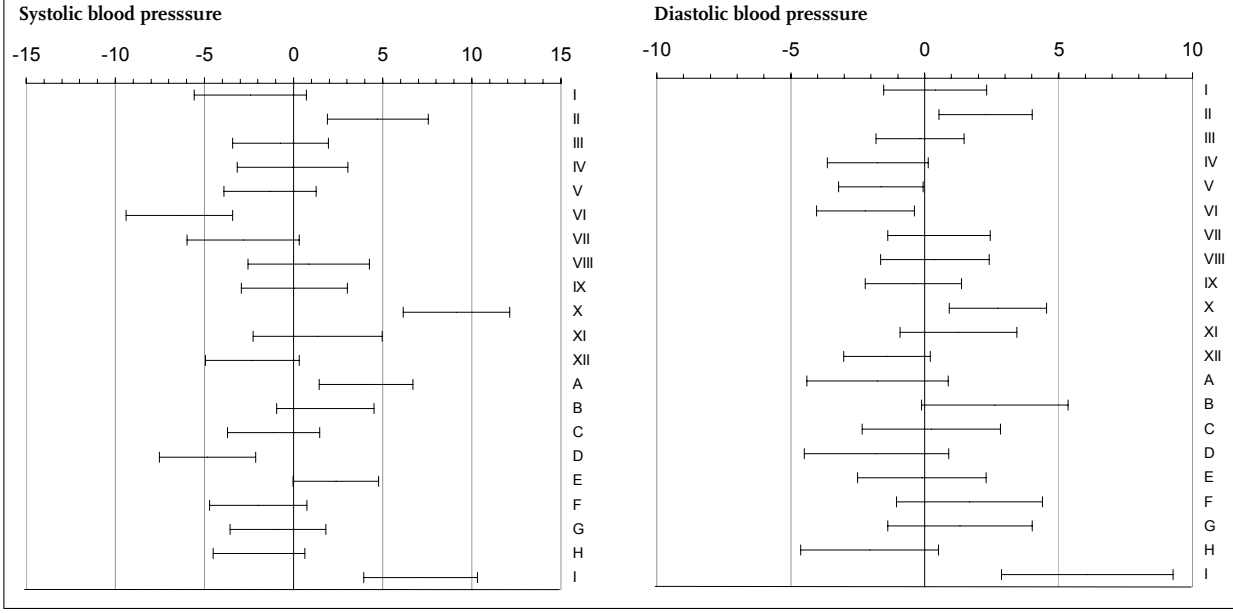
	Sphygmo-manometer + stethoscope*	Micro-phone	Oscillo-metry
Used in most inter-vention studies	Yes	No	No
Quality of hearing and stethoscope important	Yes	No	No
Stamping required*	Yes	No*	No*
Measures SBP and DBP	Yes	Yes	No
Measures MAP and calculates SBP/DBP	No	No	Yes
Sensitive to all kinds of bias**	Yes	No	No
Regular instruction and training needed	Yes	Yes	Hardly
Precision of bladder placement crucial	Yes	Yes	No
Bladder easily replaced after interruption	No	No	Yes

***Mercury is the gold standard: stamping is not needed, but normal regular inspection is useful; the mercury reservoir is filled sufficiently at zero level, the mercury tubes should be clean and there should be no leak in the air hoses. When an anaeroid sphygmomanometer is used besides the inspection as stated above also stamping is necessary at regular intervals, at least yearly. Whether the oscillometric and microphone devices need regular stamping is not yet known; regular inspection is of course useful (air hoses, batteries, printer etc.)**

****At least three kinds of bias: 1) digit preference, 2) the first reading influences the next etc., 3) memory of the results of the previous visit.**

SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure.

Figure 3. *The mean systematic deviation and the accompanying 95% confidence intervals for the 12 participating trained physicians (roman digits I to XII, upper part) and the same for the eight devices (A-I , lower part)[7], device I was a non-validated polse device*



DOES THE FUTURE BELONG TO THE OSCILLOMETRIC PRINCIPLE?

Despite the disadvantages mentioned above, there are important advantages to oscillometry, as listed in *table 3*. When, in the near future, the algorithms are improved and with the increase of home and self measurement of BP the digitalised oscillometric devices will win the competition. In *figure 3* an extra argument is demonstrated to illustrate this. The figure shows the individual means and 95% confidence intervals of BPs taken by 12 general practitioners well trained in measuring BP. BPs were measured in about 1200 patients.[7] The sometimes huge differences lead to pessimism about BP measurement by doctors and the effects of special training in BP measurement. It is tempting to conclude that in BP measurement the variation between doctors is as great as or even greater than the variation between devices, even though not all devices perform adequately. If the development in home and self measurement of BP continues, the future for oscillometric devices is bright, provided only devices that have fulfilled the criteria for accuracy according to the international guidelines are used.[8]

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ERRATA

In the special report 'Treatment of chronic hepatitis C virus infection – Dutch national guidelines', by J. de Bruijne *et al*. as published in Neth J Med. 2008;66(7):311-22, the dosing information of ribavirin was translated incorrectly. On pages 316 and 317, it should read 'weight-based ribavirin daily (1000 mg for <75 kg, 1200 mg for ≥75 kg)' instead of '800 mg ribavirin daily'. Please find below the correct information.

Antiviral therapy of HCV genotype 1

The treatment of HCV genotype 1 consists of the administration of peginterferon-α-2a 180 µg/week in combination with weight-based ribavirin daily (1000 mg for <75 kg, 1200 mg for ≥75 kg) or peginterferon-α-2b at a weekly dose of 1.5 µg/kg in combination with weight-based ribavirin (800 mg from ≤65 kg, 1000 mg from 65 to 85 kg, 1200 mg from 85 to 105 kg and 1400 mg from ≥105 kg) (*tables 7* and *8*).

Antiviral therapy of HCV genotype 4

The treatment of HCV genotype 4 consists of the administration of peginterferon-α-2a 180 µg/week in combination with weight-based ribavirin daily (1000 mg for <75 kg, 1200 mg for ≥75 kg) or peginterferon-α-2b at a weekly dose of 1.5 µg/kg in combination with weight-based ribavirin (*tables 7* and *8*).

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REVIEW

Hodgkin's lymphoma: news from an old disease

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KEYWORDS

Hodgkin, lymph node, lymphoma

INTRODUCTION

In 1832, Thomas Hodgkin reported a remarkable clinical condition characterised by enlargement of the lymph nodes and spleen, not compatible with known infectious disorders.[1] In 1856, Samuel Wilks published a series of 15 cases with similar features.[2] He suggested to name it Hodgkin's disease, after appreciating that Thomas Hodgkin had been the first to describe this entity. Recently, almost 150 years later, the term Hodgkin's disease was renamed Hodgkin's lymphoma (HL) according to the new World Health Organisation (WHO) classification of lymphoid neoplasms.[3] The new classification recognises the fact that this disorder belongs to the large range of malignant lymphomas.

Today, HL is one of the best curable malignancies in adult patients. The treatment has evolved from the first temporary successes with local radiotherapy (RT) via wide-field RT to a sophisticated combined modality approach of restricted chemotherapy and limited RT. However, surviving patients may suffer from long-term treatment-induced adverse effects, especially attributable to wide-field RT. Risk-adapted therapy according to prognostic factors is being tested intensively and an optimistic look to the future unveils individually tailored treatment programmes. Some of the major advances in the management of patients with HL are discussed here.

EPIDEMIOLOGY

In the Netherlands, yearly approximately 350 patients are diagnosed with HL. The incidence has been rather stable during the last decades. Some data suggest that the incidence in young adults in developing countries is rising while stabilising in Western countries.[4] Though the lowest incidence has been reported among people from Asian descent, recent data from Japan show an increasing incidence. Moreover, in Chinese immigrants in British Columbia the incidence of HL is higher than that in the Chinese population in Hong Kong, suggesting that environmental and lifestyle factors play a role in the pathogenesis.[5] The incidence in immune-compromised patients, e.g. those with organ and stem cell transplantation, and those with autoimmune diseases with their modern, intensified treatments, is rising. Remarkably, in human immunodeficiency virus infected patients the incidence of non-Hodgkin types of lymphomas is decreasing after the introduction of highly active antiretroviral therapy (HAART) while that of HL appears to rise.[6] The role of the Epstein-Barr virus (EBV) in the pathogenesis is still controversial (a detailed discussion is beyond the scope of this article). The genetic susceptibility to HL is corroborated by the almost hundredfold increased risk in identical twin siblings of a twin with Hodgkin's lymphoma.[7] Recently a polymorphism in the interleukin-12 expression regulating gene was found in co-twins of patients with HL suggesting a possible attribution to the increased Hodgkin susceptibility.[8]

PATHOLOGY

The giant multinucleated tumour cell first described by Sternberg and Reed in the early 20th century, has long obscured its origin. At present, there is no doubt that this Reed-Sternberg (RS) cell is a B-cell lymphocyte, though a peculiar one.[9] The cell does have rearranged immunoglobulin genes in line with its (post)germinal centre origin. However, the cell is largely incapable of producing immunoglobulins (Ig). It has lost typical B-cell

markers such as CD20 and CD79a, but expresses such antigens as CD15 and CD30. The expression of functional Ig genes is prevented by crippling mutations in the rearranged Ig genes, but many cases have intact rearranged genes so the crippling mutations do not represent the whole story. In addition, disturbed B-cell transcription factors are held responsible for the absence of a classic B-cell phenotype. In a 'normal' situation the defective B cells would undergo apoptosis. This Fas-mediated process is antagonised by c-flice-inhibiting protein that is overexpressed by the RS cell. Apart from this mechanism, the RS cell has a constitutive activation of nuclear factor kappa B (NFκB) leading to enhanced proliferation. A role for EBV is suggested in this respect via its activation of NFκB through CD40. Another cause for the overexpression of NFκB is a defect in the inhibitory work of inhibitory kappa B factor (IκB) especially in EBV-negative cases in which fatal mutations in the IκB gene have been demonstrated. In addition, amplifications on chromosome 2 have been found leading to activation of NFκB. All these findings shed some light on the pathogenesis of HL but much remains to be clarified. The crucial role of the abundant inflammatory infiltrate in the involved lymph node composed of T and B cells mixed with neutrophils, macrophages, eosinophils and mast cells, is being increasingly recognised. For its growth and proliferation the RS cell appears to be dependent on this network of cytokine and chemokine producing cells. The RS cells actively produce cytokines thereby attracting the immune cells.[10] Proteomics analysis of cell culture supernatants of HL cell lines revealed a possible role for such proteins as fractalkine, CD150, interleukin-25 and thymus-and-activation-regulated chemokine (TARC) amongst others. Some of the identified proteins, especially TARC, showed elevated levels in patients plasma and could well serve as a biomarker of the activity of the disease.[11] Differences between individual patients in these complex interactions may be responsible for the diversity in clinical presentation and course of the disease, opening avenues for targeted treatment approaches.

Classical HL has four histological subtypes. The nodular sclerosis variant is most common, comprising 80 to 90% of all cases, the mixed cellularity variant represents 10 to 15% of the cases, the lymphocyte-rich classical HL variant 2 to 5% and the lymphocyte-depleted ('poor') type is extremely rare. *Table 1* summarises the characteristics of the peculiar phenotype of the RS cell. Classical HL clearly differs from the nodular lymphocyte predominant type of HL (NLPHL), also known as *nodular paragranuloma*. This separate entity displays a distinct B-cell pattern, is almost always EBV negative, is most frequently localised in only one or two lymph node areas and can be treated with radiotherapy alone (*table 1*). Nevertheless, relapses occur frequently in contrast to classical HL. Especially in cases with more extensive disease and/or significant B symptoms, special awareness for the (co)-presence of a T-cell rich B-cell lymphoma or other type of B-cell non-Hodgkin's lymphoma is warranted. Suspected lesion(s) should be biopsied and even a complete extirpation of the originally involved lymph node should be considered, if it has not yet already been completely removed, in view of the major therapeutic consequences.

Table 1. *Immunohistochemical characteristics of classic Hodgkin's lymphomas (HL) vs the nodular lymphocyte predominant type (NLPHL)*

Characteristic	Classic HL	Nodular lymphocyte predominant HL (nodular paragranuloma)
Pattern	Nodular, diffuse, interfollicular	Nodular, at least partly
Tumour cells	Reed-Sternberg; mononuclear and lacunar cells	L&H/popcorn cells, scarce or no Reed-Sternberg cells
Fibrosis	Often	Rarely
CD15	+	-
CD30	+	-
CD20	-/+	+
CD45	-	+
EMA	-	+
EBV (in RS cells)	+ (50%)	-
Ig genes	Rearranged, clonal, fatal mutations, no/few Ig	Rearranged, clonal, ongoing mutations, Ig production

L&H = lymphocyte and histiocyte; EMA = epithelial membrane antigen; EBV = Epstein Barr virus; Ig = immunoglobulin.

IMAGING

The most important development in the imaging of HL is the 2-^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan. Conventional staging is still based on computed tomography scans combined with clinical information and histological bone marrow examination resulting in the Ann Arbor stage (I-IV) of the disease. The FDG-PET scan is based on the principle that malignant tumours have increased uptake of glucose compared with normal tissue. No large series are available to precisely define sensitivity and specificity in the staging of HL because of the lack of comparison with the golden standard, e.g. histological proof of suspected lesions.[12,13] One step ahead is the combined FDG-PET/CT technique that provides anatomical correlates on CT for positive FDG-PET findings, thereby probably increasing its reliability. Hutchings *et al.* reported upstaging of 17% and downstaging of 5% in a series of 61 patients using combined FDG-PET/CT.[14] Thanks to improvements in CT imaging and the additional CT-PET techniques, Ann Arbor stage I/II disease in 2008 is not identical to the stage I/II in 1970. The FDG-PET scan has already been

introduced into clinical practice without a rigorous testing of its precise role. The key issue is whether a change in staging modifies the treatment that should be given and whether such change leads to a better outcome. In patients with stage I/II disease the extent of the RT fields can be influenced, and in patients moving from early to advanced stages more prolonged chemotherapy would be instituted. In Hutchings *et al.'s* series, the stage migration would have resulted in a change in treatment in only 7% of the patients (all moved from early to advanced stage).[14] Nevertheless, we should recognise that FDG-PET scans will be increasingly used in the staging of patients and will lead to adaptations in the clinical management of the patients.

The more so, since new international guidelines for assessment of response to therapy in HL have been published.[15] In these response criteria, a FDG-PET scan response assessment is mandatory to evaluate the response at the end of treatment. Preferably, this FDG-PET scan should be performed four to six weeks after completion of treatment to avoid false-positive results. Though a pretherapeutic scan is not mandatory according to the guidelines, it is strongly recommended since the post-treatment interpretation of response by FDG-PET is facilitated by comparison with a pretherapeutic scan. So, we do need a FDG-PET scan at the start of treatment as well. The exciting prospects of interim response assessment (after two to three cycles of chemotherapy) by FDG-PET scan are discussed under Current and future directions.

We should keep in mind that the interpretation of an FDG-PET scan requires experienced nuclear medicine physicians and a multidisciplinary clinical consultation round. If PET-positive lesions are not recognised earlier on CT scans, the CT scans should be revised looking for an anatomical substrate for the PET-positive lesions. If not evident, the lesion should not be automatically considered as tumour positive and a histological biopsy specimen of the suspected area should seriously be considered.

CHEMOTHERAPY

The combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is the current standard chemotherapy (*table 2*). The development of ABVD stems from the 1970s,[16] but it was the result of the Intergroup randomised trial comparing ABVD with hybrid MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone/ doxorubicin, bleomycin, dacarbazine), published in 2003, that established ABVD as the preferred treatment.[17] Although there was no significant difference in efficacy between the two treatment arms with a five-year freedom-from-treatment failure (FFTF) rate of 63 *vs* 66% and an overall survival (OS) of 82 *vs* 81% respectively, the second malignancy rate was higher in the hybrid arm, favouring the use of ABVD. In addition, the switch from the classic alkylating agent-based MOPP or MOPP-like regimens to the anthracycline-based ABVD and its variants reduces the risk of infertility. Nevertheless, ABVD is far from perfect. Dacarbazine is highly emetic and can cause severe phlebitis. Bleomycin gives rise to pulmonary toxicity with occasional, but consistently occurring, pulmonary toxic deaths. Last but not least, 25 to 35% of patients with advanced disease fail to respond to ABVD and will require intensive salvage treatment with uncertain outcome. Diehl and the German Hodgkin Study Group (GHSG) developed a dose-intense multidrug regimen.[18] The resulting dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) schedule was designed to significantly increase early remission rates and to decrease the frequency of primary progressive and relapsing disease (*table 2*). There is no doubt that this regimen is one of the most active drug combinations, with an 82% FFTF and 86% OS at ten years. However, this regimen is not only anthracycline-based but includes alkylating agents as well. Thus, we will encounter untoward effects of the latter, such as second leukaemias and infertility. This has led to adaptations to the original escalated BEACOPP regimen. An initial four cycles of escalated dosed BEACOPP followed by four cycles of baseline-dosed BEACOPP appears to be as effective as the eight cycles of escalated BEACOPP, as suggested by the preliminary analysis of the GHSG HD12 study.[19] In the recently completed GHSG HD15 study, eight

Table 2. *Doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) chemotherapy*

ABVD (cycle length 28 days)

Drug	mg/m²	Route	Days
Doxorubicin	25	iv	1 and 15
Bleomycin	10	im/iv	1 and 15
Vinblastine	6	iv	1 and 15
Dacarbazine	375	iv	1 and 15

BEACOPP (cycle length 21 days)

Drug	mg/m²		Route	Days
	Baseline	Escalated		
Bleomycin	10	10	im/iv	8
Etoposide	100	200	iv	1, 2, 3
Doxorubicin	25	35	iv	1
Cyclophosphamide	650	1250	iv	1
Vincristine	1.4 (max. 2.0)	1.4 (max. 2.0)	iv	8
Procarbazine	100	100	orally	1-7
Prednisone	40	40	orally	1-14
G-CSF		+	sc	8+

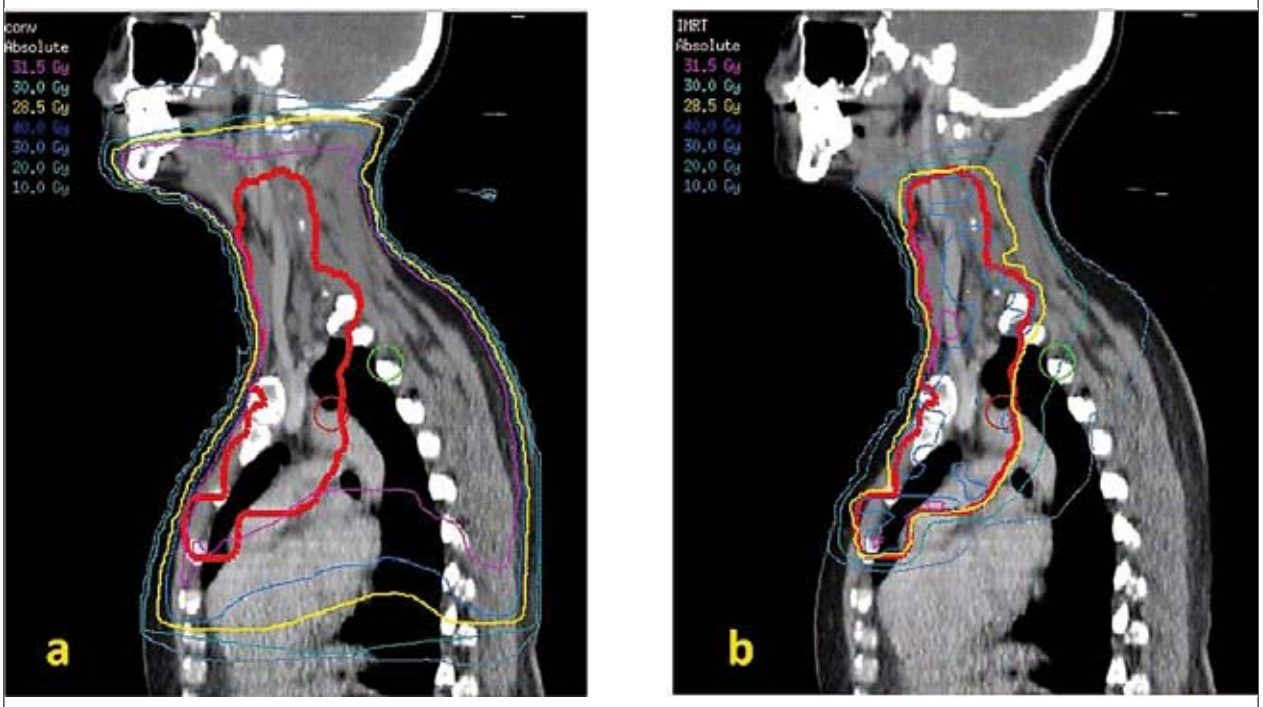
G-CSF = granulocyte-colony stimulating factor: dose dependent on product given.

cycles of escalated BEACOPP were randomly compared with six cycles of the same regimen and with eight cycles of BEACOPP14, the latter being a BEACOPP variant with baseline doses but given at a 14-day rather than 21-day interval. Results have to be awaited, especially with regard to toxicity.

RADIOTHERAPY

Radiotherapy is still the most efficacious single-agent treatment of HL. But the successful wide-field applications such as mantle field, inverted Y or (sub)total nodal irradiation, have their price in terms of second infield malignancies, and cardiovascular complications.[20] Combination chemotherapy eradicates not only clinically evident but also microscopic disease. Therefore, the large RT fields could be reduced to what are known as involved fields, e.g. only the initially involved lymph node areas, in the setting of combined modality treatment consisting of chemotherapy plus RT. As a result, the prophylactic irradiation of presumably unaffected nodal areas became redundant. In appreciating the high efficacy of chemotherapy, RT can probably be reduced even further. Better imaging techniques including 3D CT scan and FDG-PET scan allow more precise targeting and modelling of RT. Girinsky *et al*. have nicely demonstrated the potentials of reduction of the involved field principle to the involved node technique in which only the initially involved nodes rather than the involved field are being irradiated.[21,22] *Figure 1* shows the reduction in delivered RT to a neck nodal mass when irradiated according to the IF-RT technique compared with the IN-RT principle. This approach with allegedly less toxicity is now being applied in the current Intergroup H10 study of the EORTC Lymphoma group, the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) and the Intergruppo Italiano di Linfomi (IIL) (see later under Current and future directions). Although attractive, a special note of warning should sound. By reducing the RT field, the exact localisation of the initially involved lymph nodes has become crucial, for the remaining nodes in the respective lymph node area will not be irradiated. Here, we need – more than ever – a close multidisciplinary cooperation between radiation oncologist, haematologist, radiologist, and nuclear medicine physician to exactly define the targets of treatment. A judicious interpretation of combined FDG-PET/CT scan imaging will probably help to come up to our expectations of a safe reduction in RT fields.

Figure 1. *Sagittal view of a patient with clinical stage II Hodgkin's lymphoma with localisations in neck and mediastinum*



The thick red line encompasses the pre-chemotherapy involvement with a 1 cm margin. The CT scan is taken for radiotherapy treatment purposes after chemotherapy.
A) Dose distribution when the patient is irradiated according to the involved field principle.
B) Dose distribution when the patient is irradiated according to the involved node principle with an intensity modulated radiotherapy technique. Notice that the coverage of the target volume (red contour) in both plans is good (yellow line, 95% of prescribed dose). The involved node technique gives a considerable sparing of normal tissues (heart, lung, neck, mouth).

SURVIVORSHIP

In appreciating survivorship for patients treated in the modern era, we should take into account that our knowledge of long-term complications is based upon observations after extended-field RT and alkylating chemotherapy regimens. Second malignancies mainly concern breast and lung cancer. Female patients who received RT to mediastinal and/or axillary nodes prior to the age of 30 have a 2.5 to >5 times elevated risk of developing breast cancer.[23] The risk appears to be most pronounced in women who remain premenopausal for >15 years after treatment for HL, whereas those who became postmenopausal within five years after treatment had a significantly lower risk of secondary breast cancer.[24] The protective effect of (alkylating) chemotherapy-induced menopause will probably disappear with increasing use of the more ovary-friendly ABVD. Elevated risks of lung cancer are reported after RT but also after alkylating agents while smoking even further increases the relative risk to >9.[25,26] A recent Dutch cohort study estimated a three to fivefold increased incidence of several types of cardiac diseases after RT and anthracycline-containing chemotherapy compared with the general population, with the highest risks observed in the youngest patients at diagnosis of HL.[27,28] Patients irradiated to the neck have an increased risk of stroke.[29] Male infertility has been recently readdressed by the GHSG and the large series of the EORTC highlighting the high incidence of >93% of elevated FSH levels after alkylating agents, especially BEACOPP,[30] *vs* only 8% after ABVD.[31]

Awareness of these late effects urges the need for guidelines for standardised follow-up examinations in long-term survivors. The yearly mammographic examinations for female patients irradiated at young age is already standard and starts eight to ten years after RT. According to the Dutch guidelines an MRI should be performed as well for screening in this high-risk group of patients. Yearly thyroid-stimulating hormone measurements for detection of irradiation-induced hypothyroidism is done in most patients. The relevance of screening and/or early intervention strategies for cardiovascular diseases is less evident and awaits further research.

HOW TO MANAGE?

Favourable Ann Arbor stage I/II

In patients with stage I/II disease we can identify a subset with favourable pretreatment criteria (40 to 45% of patients) and a group with unfavourable characteristics (55 to 60%) (*table 3*). The cornerstone of the treatment for patients with stage I/II HL is the combined modality approach. On behalf of the EORTC and GELA, Fermé *et al*. reported in 2007 on the H8 trial for patients with stage I/II HL.[32] Patients with favourable stages I/II were randomised between subtotal nodal irradiation (the standard treatment at the time the trial started in 1993) and the combined modality regimen consisting of three cycles of MOPP/ABV hybrid (the standard chemotherapy at the time the trial started) followed by 36 Gy involved-field RT (IF-RT). After a median follow-up of 92 months the combined modality treatment proved superior, not only in terms of event-free survival (EFS) but also in terms of OS: at ten years an EFS of 68 *vs* 93% and an OS of 92 *vs* 97% respectively (p=0.001). Excellent results for sure, but how should these data be handled in 2008? MOPP/ABV hybrid is no longer standard chemotherapy because of the increased risk of secondary leukaemias and infertility. ABVD should be given instead. But in this limited disease situation, even three cycles of ABVD might be too toxic. In the most recent GHSG HD13 study the relative merits of the individual components of the ABVD regimen have been randomly compared, e.g. two cycles of ABVD *vs* AVD *vs* ABV *vs* AV. Can bleomycin be removed from the ABVD regimen? This is the crucial question but final results are not yet available.

Whereas the chemotherapy adaptations seem to reach a final endpoint quite soon, the radiotherapy component of the combined modality is being adapted as well. There are some preliminary data that suggest that the dose of RT can be reduced from 30-36 to 20 Gy. However, both in the EORTC/GELA H9 study and in the GHSG HD10 study, the FFTF curves of the 30-36 Gy *vs* those of 20 Gy appear to diverge in favour of the higher dose of RT after prolonged follow-up periods of more than six years.[33,34] Since the extremes in the Kaplan-Meier survival curves should be interpreted with caution, no final conclusion can

Table 3. *Definition of favourable and unfavourable stage I/II Hodgkin's lymphoma*

	European Organisation for Research and Treatment of Cancer	German Hodgkin Study Group
Risk factors	a) Large mediastinal mass b) Age ≥50 years c) ESR ≥50 without B symptoms or ≥30 with B symptoms d) ≥4 nodal areas	a) Large mediastinal mass b) Extranodal disease c) ESR ≥50 without B symptoms or ≥30 with B symptoms d) ≥3 nodal areas
Favourable	CS I-II (supradiaphragmatic) without any risk factor	CS I-II without any risk factor
Unfavourable	CS I-II (supradiaphragmatic) with at least 1 risk factor	CS I or CS IIA with at least 1 risk factor CS IIB with c) or d) but without a) and b)

ESR = erythrocyte sedimentation rate; LP = lymphocyte predominance; NS = nodular sclerosis; CS = clinical stage.

be drawn yet from these large randomised trials. A dose of 30 Gy is still standard. Can RT be omitted in the early-stage situation? The answer is no. In the EORTC/GELA H9F trial randomising between no RT after six cycles of the ABVD chemotherapy variant EBVP (epirubicin, bleomycin, vinblastine, prednisone)[35] and IF-RT, the no-RT arm had to be closed prematurely because of a significantly higher incidence of relapses/progressions compared with the RT arms.[33] The conclusion from this H9F trial is that RT cannot be omitted after EBVP chemotherapy in favourable stage I/II disease. That does not necessarily mean that RT is always required after other chemotherapy such as ABVD, but this question should be readdressed in a randomised clinical trial as is being done in the H10 trial (see below). In the meantime the combined modality approach remains standard treatment for favourable stages I/II.

Unfavourable Ann Arbor stage I/II

In the abovementioned EORTC/GELA H8 study the patients with unfavourable stages I/II were randomised between three different combined modality approaches: six cycles of MOPP/ABV + 36 Gy IF-RT *vs* four cycles of MOPP/ABV + 36 Gy IF-RT *vs* four cycles of MOPP/ABV + 36 Gy subtotal nodal irradiation.[32] After a median follow-up of 92 months no differences between the three treatment arms were seen, neither in EFS nor in OS (around 85%). In this subset of patients there is room for improvement of tumour control. In an attempt to improve the outcome, the successor EORTC/GELA H9 trial randomly compared four cycles of ABVD to four cycles of baseline dose BEACOPP, both followed by 30 Gy IF-RT. In the first preliminary analysis no significant differences in outcome were noted.[33] Similarly the GHSG HD11 trial failed to show an improvement in outcome after baseline-dosed BEACOPP as compared with ABVD in this subset of patients.[19] Therefore, the combined modality consisting of four cycles of ABVD followed by 30 Gy IF-RT remains the standard treatment.[36]

Ann Arbor stage III/IV

Patients with advanced disease receive six to eight cycles of ABVD. In case of a CR after chemotherapy, additional RT is not required as shown in the EORTC 20884 trial.[37] In case of residual disease after six cycles of chemotherapy additional involved field RT is given. With this strategy a seven-year FFTF of >70% and OS of >80% have been reached.[38]

In the landmark GHSG HD9 randomised clinical trial, 1186 evaluable patients have been randomised between the ABVD variant COPP/ABVD, the baseline-dosed BEACOPP and the escalated-dosed BEACOPP schedule.[18] Most patients received additional 30 Gy RT to initially bulky masses (defined as >5 cm) or residual disease after chemotherapy. The initially reported significantly better outcome for patients treated with escalated BEACOPP still holds after prolonged follow-up: at ten years FFTF are 64% (COPP/ABVD), 70% (BEACOPP baseline) and 82% (escalated BEACOPP) and OS rates of 75, 80 and 86% respectively. The hypothesis of avoidance of early treatment resistance by starting with the dose-intense regimen right away appears to be corroborated by the differences in induction failure rates between the three treatment arms: 25, 12 and 4% respectively. The results also suggest that escalated BEACOPP should become the new standard chemotherapy schedule instead of ABVD. However, some reticence is justified. The schedule is manageable but toxic. It requires haematopoietic growth factor support, more frequent day care facilities because of the administration schedule of the chemotherapy, it includes alkylating agents with the increased risk of infertility and second leukaemias, and last but not least, awaits confirmation of its supposed enhanced efficacy from other randomised trials. One of these trials, the Italian cooperative group HD2000 GISL study, was recently reported in a preliminary analysis.[39] A three-arm comparison was made between six cycles of ABVD, COPPEBVCAD and BEACOPP (first four cycles in escalated dose followed by two cycles in baseline dose). RT was delivered to initially bulky or residual masses. The analysis on 270 evaluable cases showed no statistically significant differences in CR rates after chemotherapy: 82, 79 and 90% respectively. After a median follow-up of 39 months, the three-year progression-free survival was significantly better for the BEACOPP arm as compared with ABVD and COPPEBVCAD: 90 *vs* 72 *vs* 80% respectively. No significant differences in OS were observed. The BEACOPP regimen was associated with higher rates of severe infections, 13 *vs* 1 and 3% respectively. No definite conclusions can be drawn yet. Therefore, the results of the ongoing Intergroup trial 20012 led by the EORTC, randomly comparing eight cycles of ABVD with four cycles of escalated-dosed BEACOPP followed by four cycles of baseline-dosed BEACOPP, are eagerly awaited. This study addresses the 'poor-risk group' of advanced stage patients, e.g. those with an International Prognostic Score of >2 factors (*table 4*).[40] Details on the frequency distribution of the patient numbers and their respective outcome dependent on the number of adverse factors are also given in *table 4*. In contrast to the GHSG and the Italian study, in the EORTC trial no RT is given to patients who reach a CR on chemotherapy.

Another remarkable issue in comparing ABVD and escalated BEACOPP should be taken into account, as Horning correctly pointed out in the 2007 educational session of the American Society of Hematology.[41] One of the presumed reasons for the success of escalated BEACOPP is the increased dose intensity pushed to the limit by support of haematopoietic growth factors. All studies with ABVD are based upon the rather conservative

Table 4. *International Prognostic Score for patients with stages III/IV Hodgkin's lymphoma*

Number of factors	% of patients	5-year progression-free survival %
0	7	84
1	22	77
2	29	67
3	23	60
4	12	51
≥5	7	42

The seven clinical prognostic factors are: age ≥45 years; male sex; Ann Arbor stage IV disease; albumin <40 g/l; haemoglobin <6.5 mmol/l; leucocyte count ≥15 x 10^9/l; lymphocyte count <0.6 x 10^9/l.

dose adaptation guidelines from the original reports resulting in frequent dose adaptations and/or delay in starting new cycles. Recent data show that ABVD can be given at 100% dosage despite neutropenia and without growth factor support.[42] In a single centre experience, two physicians treated their patients (n=61) with ABVD in full doses irrespective of neutrophil counts. The overall dose intensity was 99.1%. The incidence rate of febrile neutropenic episodes was only 0.4% in a total of 682 ABVD administrations, but – admittedly – under coverage of pneumocystis and *Candida* prophylaxis. The five-year EFS and OS for this group of patients (57% early stage and 43% advanced stages), was 93 and 97% respectively. Why these data? The question arises whether comparison of the outcome after a conservative dose-adaptation guided ABVD schedule and that after the escalated BEACOPP schedule is fair. Could the results of ABVD improve just by a full-dose strategy, despite neutropenia? If so, one could avoid the toxicity of the alkylating agents in the BEACOPP schedule. This has not been tested so far. Possibly, the abovementioned ongoing EORTC Intergroup study will shed some light on this issue.

Therefore, ABVD is still the standard chemotherapy for advanced stage patients. RT is only indicated in case of PR after chemotherapy. One probably should give the full dose of ABVD despite neutropenias. The subgroup of patients to benefit from the intense escalated BEACOPP still needs to be defined.

CURRENT AND FUTURE DIRECTIONS

Risk-adapted approaches are being explored intensively in current randomised clinical trials, in pursuit of the balance between cure and complication-free survivorship. Two main questions arise. First, do we have new reliable and reproducible indicators for risk adaptation of our treatment? We cannot expect that after so many examples of clinical prognostic indices, any new clinical pretreatment prognostic variable will be identified. Treatment-related factors are probably more informative. Old data indicated that patients with an early response to chemotherapy, e.g. CR after two to four cycles of chemotherapy, have a better outcome. In fact, the EORTC approach administering a total of only six cycles of chemotherapy in advanced stages in case of an early CR (after four cycles) and a total of eight cycles in case of late CR (after six cycles) is based on these data.[43,44]

The definition of a CR based on conventional imaging is troublesome in HL. FDG-PET imaging will probably help us out. In the new criteria for assessment of response after completion of treatment, a CR[15] implicates a negative PET scan for all lesions whereas a PR indicates a decrease of >50% of the lesions with a least one PET-positive lesion. In the recently completed GSHG HD15 trial for patients with advanced stages, only those with a PR based on conventional imaging but still PET positive receive additional RT. Final results have to be awaited. The spectacular results of the combined Italian and Danish experience with the predictive value of an early interim FDG-PET scan in patients with advanced disease hold great promise.[45] Patients received a predefined treatment, usually six to eight cycles of ABVD, followed by RT. After two cycles of chemotherapy an FDG-PET scan was performed but no treatment changes were allowed on the basis of the PET results. Fifty out of 260 patients (20%) were FDG-PET positive after two cycles of chemotherapy and 210 (80%) already FDG-PET negative. After a relatively short follow-up of two years, 43/50 (86%) of the PET-positive patients progressed or relapsed whereas only ten of the 210 PET negatives (5%) progressed or relapsed (p<0.001). It is almost too good to be true!

Second, is there any evidence to support a strategy of escalating treatment when needed, or de-escalating treatment when possible, based on the early PET response? The answer is no. Should all patients with advanced disease start with the intensive escalated BEACOPP regimen and then have a decrease in intensity in case of an early negative PET scan? Such an approach would integrate the theoretical advantage of avoiding early treatment resistance by treating as intensively as possible right from the start and by reducing the burden of subsequent treatment based on early PET response. Probably, a majority of patients would not have needed the two intensive escalated BEACOPP cycles and would have done well with ABVD, thereby avoiding the toxicity of the intensified treatment. The opposite approach is to start with a less intense treatment – for example ABVD – and to escalate in case of a positive early FDG-PET scan. This attitude would spare the initial toxicity of escalated BEACOPP but harbours the theoretical risk of having induced resistance that cannot be overcome anymore by switching to escalated BEACOPP.

We are dealing with theoretical – though plausible – assumptions and their validity should and can only be addressed in carefully designed randomised trials. *Table*

Table 5. *Current and forthcoming randomised trials in untreated patients with Hodgkin's lymphoma*

Trial	Patient groups	Trial design and randomised treatments
NCRN UK (*start 2003*)	IA/IIA, no mediastinal bulk	ABVD x 3, then PET response, • if PET negative: A. IF-RT B. no further treatment • if PET positive C. ABVD x 1 + IF-RT
EORTC/GELA/IIL H10 stage I/II (EORTC #20051) (*start 2006*)	I/II favourable	A. ABVD x 3 + IN-RT B. ABVD x 2, then PET response, • if PET negative: ABVD x 2, no RT • if PET positive: esc. BEACOPP x 2 + IN-RT
	I/II unfavourable	C. ABVD x 4 + IN-RT D. ABVD x 2, then PET response, • if PET negative: ABVD x 4, no RT • if PET positive: esc. BEACOPP x 2 + IN-RT
GHSG HD 16 (*projected start 2008*)	I/II, no risk factors	A. ABVD x 2 + IF-RT B. ABVD x 2, then PET response, • if PET negative: no further treatment • if PET positive: IF-RT
GHSG HD 17 (*projected start 2008*)	I/II, with risk factors	A. ABVD x 4 + IF-RT B. ABVD x 4 + IN-RT C. EACOPP(14) x 4 + IF-RT D. EACOPP(14) x 4 + IN-RT
EORTC Intergroup #20012 (*start 2002*)	III/IV poor risk (>2 risk factors IPS)	A. ABVD x 8 B. esc. BEACOPP x 4 + base BEACOPP x 4
GHSG HD 18 (*projected start 2008*)	III/IV	Escalated BEACOPP x 2, then PET response, • if PET negative: A. esc. BEACOPP x 6 B. esc. BEACOPP x 2 • if PET positive: C. esc. BEACOPP x 6 D. esc. BEACOPP x 6 + rituximab

NCRI UK = National Cancer Research Network United Kingdom; EORTC = European Organisation for Research and Treatment of Cancer; GELA = Groupe d'Etudes des Lymphomes de l'Adulte; IIL = Intergruppo Italiano di Linfomi; GHSG = German Hodgkin Study Group; HD = Hodgkin's disease; I/II/III/IV = Ann Arbor stages; IPS = International Prognostic Score; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; esc. =escalated; IF-RT = involved field radiotherapy; IN-RT = involved-node radiotherapy; PET = positron emission tomography.

5 summarises the leading, currently ongoing or soon to be started European initiatives. In the UK trial, the main question is whether RT can be omitted in patients with stage I/II disease without mediastinal bulk, if the PET scan has become negative after three cycles of ABVD. Importantly, this randomised trial uses the PET scan at the end of chemotherapy and does not test early PET scan-guided treatment adaptation. The concept of early treatment adaptation in patients with stage I/II disease is being tested in the EORTC/GELA/IIL Intergroup H10 trial (EORTC #20051). In this important ongoing trial patients are randomised between the standard combined modality treatment (ABVD x three followed by IN-RT for the favourable subset and ABVD x four followed by IN-RT for the unfavourable subset) and the new, early PET response adapted approach: those with a negative early PET scan (after two cycles) receive additional cycles of ABVD without IN-RT, and those with a positive early PET scan switch to the intensified escalated BEACOPP schedule followed by IN-RT. In this trial, over 1500 patients are required to demonstrate that chemotherapy alone is non-inferior to the combined modality approach in case of early PET negativity and that intensification produces better results in case of early PET positivity. The target accrual is expected to be completed in 2010, with most of Dutch centres participating actively.

The GHSG will start their new-generation studies in 2008. In patients with stage I/II disease without risk factors, patients are randomised between ABVD x 2 followed by IF-RT and ABVD x 2 without RT in case of a negative PET scan after two cycles (GHSG HD16 trial). In this design a negative PET scan after two cycles of ABVD is considered synonymous to cure but it remains to be seen whether two cycles of ABVD is sufficient treatment for stage I/II disease. In stage I/II with risk factors, the randomisation concerns a four-arm comparison between four cycles of ABVD and EACOPP (a variant of the escalated BEACOPP schedule without bleomycin and given every 14 days) followed by either IF-RT or IN-RT, the only trial comparing the IF-RT principle with the concept of IN-RT (GHSG HD 17 trial). The already mentioned ongoing Intergroup trial led by EORTC for

patients with poor-risk advanced disease comparing ABVD with escalated BEACOPP is of paramount importance in defining the standard chemotherapy schedule. This study does not incorporate PET-based decisions. In the four-arm GHSG HD18 trial all patients will start on escalated BEACOPP. Those with a negative early PET scan will go on with either the standard six cycles of escalated BEACOPP or just two additional cycles aiming at reducing toxicity in a presumed good-prognosis group. Those with an early positive FDG-PET scan will continue with the standard six cycles of escalated BEACOPP or will receive the experimental arm containing six cycles of escalated BEACOPP + rituximab, the monoclonal anti-CD20 antibody, aiming at improving efficacy by targeting the presumably CD20-positive Hodgkin stem cell, in this poor-risk group.

EPILOGUE

The avenue is opened to a risk-adapted and individualised treatment approach for patients with HL. A meticulous search for the balance between cure and toxicity is the challenge for future cooperative Intergroup efforts reflected in carefully designed randomised clinical trials. The combination of chemotherapy and radiotherapy for those who need it, chemotherapy alone if possible to avoid RT-induced late complications and intensified chemotherapy BEACOPP-like regimens reserved for those with well-defined poor-risk disease.[46] The prognosis for the small subset of patients with refractory disease is still grim and urgently awaits new effective drugs possibly acting by different pathways. New strategies for elderly patients are needed as well. Continued special attention for long-term observation remains warranted to monitor whether our current concepts indeed translate into improved survivorship. Evidence-based guidelines would be helpful in offering state-of-the-art follow-up care. The momentum is here for a national initiative integrating the evaluation of early interventions for prevention and management of complications.

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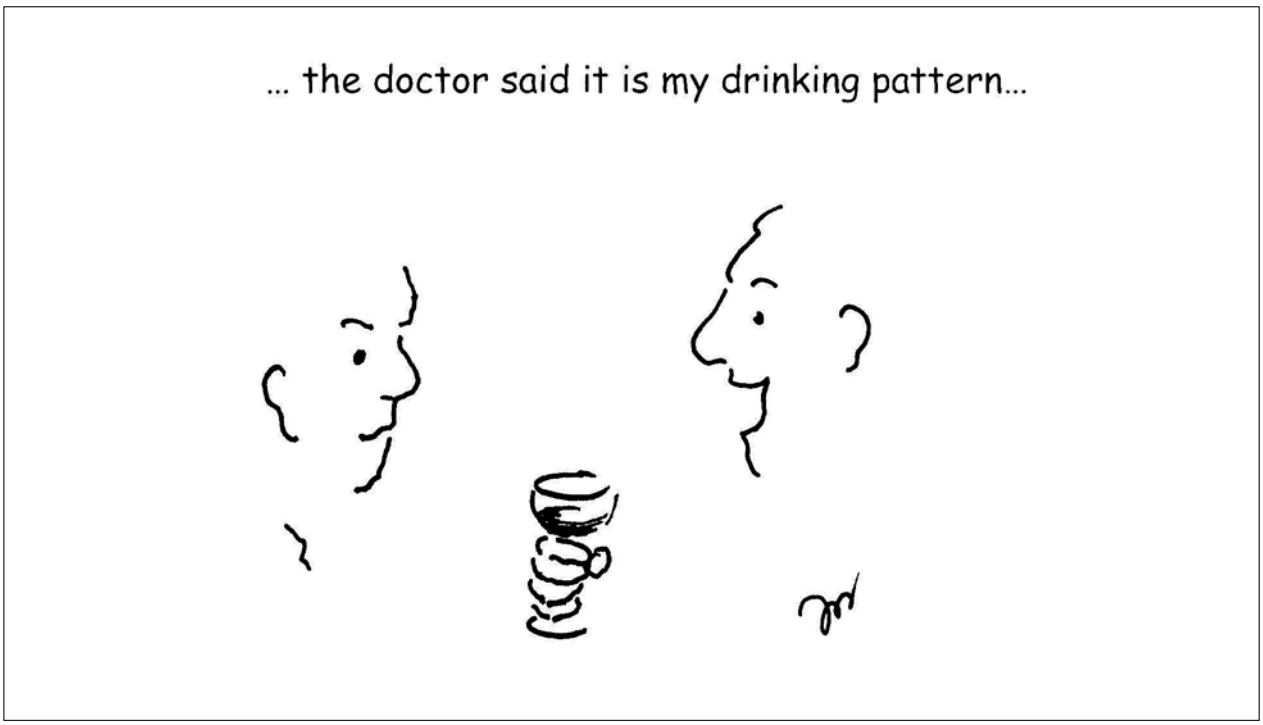

Raemaekers, et al. Hodgkin's lymphoma: news from an old disease.

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REVIEW

Cardiovascular risk is more related to drinking pattern than to the type of alcoholic drinks

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ABSTRACT

Many observational studies have shown an association between moderate alcohol consumption and a lower risk for cardiovascular morbidity and mortality. Some of these studies, whether or not inspired by the French paradox, suggest a more favourable effect of wine than of other alcoholic drinks. Certain polyphenols including the flavonoids, more abundant in red than in white wine, are held responsible for this 'bonus' effect. However, this conclusion seems premature, since no significant bioactive effect of wine polyphenols has been shown in humans so far. Furthermore, wine drinking proves to be associated with a healthier lifestyle profile than consumption of beer and liquor, and this may have a substantial influence on the outcome of studies.

In contrast to moderate drinking, incidental heavy or binge drinking is associated with an increased cardiovascular risk by influences both on the electrical conduction system of the heart and the process of atherothrombosis. Although only prospective randomised intervention trials including a sufficient number of people will give definite answers, the chances are small that they will ever be performed given the ethical and practical objections of such studies. Available data so far justify the conclusion with regard to cardiovascular risk that the pattern of drinking is of more importance than the content of the bottle.

KEYWORDS

Alcohol, binge drinking, cardiovascular risk, ethanol, wine

INTRODUCTION

Health aspects of alcohol have been debated for centuries. Alcoholic drinks have been used as restoratives, stimulants, appetizers, and even as analgesics for many of the body's aches. But alcohol consumption has also proven to be associated with liver disease, cardiomyopathy, trauma and injuries, the Wernicke-Korsakov syndrome and some forms of cancer.

In ancient and medieval times, wine and beer were part of everyday diet, because many places on earth lacked reliable sources of drinking water. Nowadays, they are mostly regarded as regular staples of modern day living and their consumption parallels the increase in welfare. During the last two decades the popularity of alcoholic drinks, especially wine, has received an extra boost because of an assumed beneficial effect on the cardiovascular system. This was first observed in observational studies comparing countries with regard to wine consumption and cardiac mortality.[1] Despite a high intake of saturated fats, a significant lower mortality rate of coronary heart disease was observed in France compared with other Northern European countries, a phenomenon which became known as the French paradox.[2] This paradox was initially explained by ingredients of the Mediterranean diet, which resulted in much attention to the potential favourable effect of wine, especially in the lay press. Most physicians and medical organisations, however, stayed critical and reserved towards the promotion of wine drinking, being aware of the other and darker side of the Janus head. Furthermore, later analyses and studies threw doubt on the superiority of red wine over other alcoholic drinks. This review focuses on the pitfalls of the studies analysing the relationship between wine drinking and cardiovascular risk. It concludes that the pattern of drinking may be more important than the content of the bottle.

THE FRENCH PARADOX, WINE AND POLYPHENOLS

From its very first description in medical literature, the 'French paradox' has been a matter of dispute. In 1992 Renaud and De Lorgeril observed a lower mortality rate of coronary heart disease in France in comparison with other Northern European countries and especially the United Kingdom, despite a similar or even higher intake of saturated fats.[2] The authors explained the paradox primarily by the characteristics of the 'Mediterranean diet', with an abundance of vegetables, fruits, olive oil, and especially red wine.

At that time there were already indications of a U-shaped relationship between alcohol consumption and mortality risk with the lowest risk in moderate drinkers.[1,3,4] But the French paradox hinted on the idea that red wines with their relatively high concentrations of flavonoids had more to offer than other alcoholic drinks.

Although our knowledge of the chemical composition of grapes has advanced greatly in the last 40 years, much still remains a mystery. The number of compounds identified in wine has increased dramatically since the development and combination of high-pressure liquid chromatography, infrared spectroscopy and mass spectrometry.[5] More than 500 compounds have been recognised in wine thus far, of which 160 are esters. The concentrations of the majority range between 10^{-1} and 10^{-6} mg/l. At these levels the individual compounds play very little or no role in the human taste perception, but collectively they may be very important. The most predominant chemical constituents of wine and grapes are water, followed by alcohol, sugars, polysaccharides, and acids. Phenols are a large and complex group of compounds of particular importance for the characteristics and quality of wines. They may come from the fruit (skins and seeds) and vine stems, production by yeast metabolism, or extraction from wood cooperage. Their concentration in white wines is much lower than in red wines. Chemically, phenols are cyclic benzene compounds possessing one or more hydroxyl groups associated directly with the benzene structure. Flavonoids are characterised as molecules possessing two phenols joined by a pyran (oxygen containing) carbon ring structure. The concentration of phenols in wines increases during skin fermentation and subsequently begins to fall as phenols bond and precipitate with proteins and yeast hulls (cell remnants). During maturation, the phenols continue to decrease, and ageing has a further effect on their reduction.

Polyphenols are not exclusive for wines but are widely present in trees, plants and vegetables, such as in tea, cacao and onions.[6-8] In nature, they exhibit a wide range of biological effects as antioxidants, antimicrobials, and modulators of various enzyme systems.[6-8] This remarkable spectrum of biochemical and cellular functions certainly holds promise and some of these effects have been shown in *in vitro* and *ex vivo* models. However, not enough is known yet about their absorption, bioavailability and bioactivity to conclude that they are indeed operative in the wine-consuming human being.

ALCOHOL AND CARDIOVASCULAR PROTECTION

Through the last two decades of the last century, a rather consistent body of epidemiological data has accumulated pointing to a 20 to 40% reduced incidence of morbidity and mortality from coronary heart disease among those who consume alcohol in moderation by comparison with abstainers.[9-20] Although alcohol consumption increases the risk of various cancers, hypertension, liver disease, unintentional injuries, and violence, the relationship between alcohol intake and all-cause mortality is U-shaped, with nondrinkers and heavier drinkers having higher risks than light and moderate drinkers.[21-27] Furthermore favourable effects have also been shown in other atherothrombosis-related disorders such as cerebrovascular accidents and some forms of dementia.[28,29] This risk reduction by alcohol can partly be explained by an increase in high-density lipoprotein cholesterol (HDL-c), but is also related to levels of fibrinogen and HbA_{1c}.[30] This association of alcohol with HDL-c levels seems related to cholesteryl ester transfer protein (CETP) polymorphism.[31] Various studies now focus on the effects of alcohol on other parts of the atherothrombotic process such as platelet function, coagulation, fibrinolysis, inflammation, oxidative stress, and gene expression.

There are, however, some serious pitfalls with observational studies. These studies might reveal a certain association between alcohol consumption and a decreased mortality, but they do not necessarily prove cause and effect. Observational studies have difficulty in allocating subjects to the intervention and control groups, as those subjects are not randomised. It is possible to correct for known confounders; however, unknown confounders or unmeasured variables still influence outcome. For instance, in the Copenhagen study with 24,000 participants, the consumers of red wine appeared to have a relative risk for cardiovascular diseases of 0.66 (95% confidence interval 0.55 to 0.77) compared with non-drinkers.[32] However, wine drinking was significantly associated with a higher IQ, a higher parental education level and a higher socioeconomic status. Therefore, wine drinking might just be an innocent bystander in the cascade that leads to cardiovascular disease or just an indication of a healthier lifestyle that might have been cardioprotective.[33] In other population studies a specific wine-related effect might be masked by

the fact that many alcohol consumers drink all types of alcohol (also beer and spirit) not allowing any conclusion on a wine effect.

To prove cause and effect, randomised and blinded trials are needed. But with alcohol such trials are hardly feasible for ethical and practical reasons. Alcohol is a potentially hazardous substance with severe side effects, danger of addiction and misuse. Secondly, consuming alcohol does not go unnoticed, making blinding of the subjects very difficult. Furthermore the follow-up should be very long, since it takes many years for atherothrombotic disorders to develop, and the number of individuals needed to follow would be substantial.

Trials that have been performed so far on human volunteers or patients, therefore, focused on surrogate endpoints for cardiovascular diseases needing less time and a limited number of individuals. Recently, two small randomised trials, both with 24 healthy volunteers, showed that alcohol consumption increased blood pressure slightly, but statistically significantly without a change in flow-mediated dilatation after only four weeks.[34,35] In 20 other healthy volunteers, red wine consumption improved antioxidant status and reduced LDL oxidation after two weeks.[36] An increase in HDL cholesterol content after four weeks was observed in another 69 volunteers.[37] Beneficial effects of alcohol consumption on lipids and cholesterol had already been shown in small randomised trials with cross-over design after three weeks.[38-41] In a study focusing on the early steps in reverse cholesterol transport no significant difference in HDL lipids could be observed between beer, wine and spirits indicating the effects only to be related to the alcohol component.[42] Only few randomised trials have involved patients with established coronary artery disease. In these patients consumption of wine did improve flow-mediated dilatation after 360 minutes of ingestion.[43] In short, randomised trials have been performed, but are often of short duration (up to four weeks) and have included few subjects (mostly 20 to 30 healthy, young volunteers). However, a longer follow-up was performed by Mezzano *et al.*, who studied the effects of the Mediterranean diet and the supplementary effects of red wine in cross-over design in 21 volunteers for 90 days and they did not find any effect on lipids or *ex vivo* platelet aggregation.[44,45]

WINE OR BEER

Several population-based studies and meta-analyses have reported the beverage-specific risk estimates for cardiovascular disease for wine and beer. They report a strong and statistically significant benefit for both beer and wine at levels of moderate consumption (defined as up to 150 ml of red wine and up to 20 grams of alcohol daily), but they find a stronger inverse association for wine (32% risk reduction) than for beer (22%).[15] Other reviews, however, found the benefits of wine to be about the same as those of beer or spirits, and state that it is unlikely that any one beverage is substantially more beneficial. It is therefore helpful to examine their results in more detail and to explore the importance of potential biases that may have influenced the findings.

The ethanol content in a serving of wine is similar to that in a serving of beer, and results from metabolic studies suggest that the effects of these beverages on lipid and haemostatic factors are similar.[46] Thus, if this apparent difference in beverage-specific relative risks is true, then components in wine other than alcohol must confer substantial additional benefit. As mentioned, several antioxidants and other compounds have been identified in red wine, but the incremental benefits of these compounds on biomarkers predictive of coronary heart disease have not been established yet.

An alternative explanation might be that beer and wine have the same physiological effect, but differences in the risk factor patterns among beer and wine drinkers might create the appearance of a difference in coronary heart disease risk.[47,48] A meta-analysis by Di Castelnuovo *et al.*[15] is instructive for further examination of these results because it outlines the important influences of individual study characteristics. Although the authors reported little difference between prospective and retrospective studies when they excluded the studies that did not simultaneously adjust for different types of alcoholic beverages (the most unbiased method to control for confounding), there was no longer a difference in the relative risk of cardiovascular disease between wine drinkers (25%) and beer drinkers (23%) compared with abstainers. These differences may be due to chance, but they do illustrate how susceptible results from meta-analyses are to a few biased studies. An additional pitfall of meta-analyses is that important covariates may not be treated equally across studies. Therefore, pooling relative risks from studies that do not equally account for other risk factors, such as smoking or dietary pattern, can exaggerate or mask differences.

This becomes especially difficult for alcoholic beverage consumption because the direction of potentially important confounders, such as a healthy diet, can be completely opposite as a result of the cultural norms of the population under study. For example, in the aforementioned Danish study, fruit and vegetable consumption was strongly associated with wine intake,[47] whereas in a French EPIC study[49] drinkers of wine consumed less fruits and vegetables. Even within the same country, the direction of confounding can differ. Contrary to the results from the EPIC study, in a separate population from France, wine consumption was associated with a better lifestyle; after controlling for diet and social class, the differential beneficial effects of wine over beer were eliminated.[50]

In other populations another type of alcohol may be the predominant drink related to a healthier lifestyle, thus showing the beneficial effect for that type of alcohol.[51]

In general, studies typically found that wine drinkers tend to have a healthier lifestyle profile than beer drinkers. Without careful control for such confounders across all studies, it is not possible to interpret the biases that may occur by pooling such estimates. The growing number of studies in recent years addressing drinking patterns and preferences should provide better insight into the importance of specific alcoholic beverages.[31,48,52-57] Regardless of the population or the distribution of beverage consumption, residual confounding by diet, physical activity, behavioural characteristics, or even psychological parameters[55] needs to be carefully addressed.

DRINKING PATTERN AND CARDIOVASCULAR DISEASE

Although light-to-moderate alcohol consumption appears to have a U-shaped relationship to cardiovascular disease and especially coronary artery disease, 'binge drinking' seems to put consumers at an increased risk for cardiovascular diseases.[58] A report by Knupfer[59] suggested that the pattern of daily light drinking is, in fact, not at all common. This study indicated that most light drinkers do not drink daily and most daily drinkers are not light drinkers; that is, consumers of two standard drinks per day.

At the other end of the spectrum, the use of the term 'binge drinking' is similarly confusing. It may refer to heavy drinking on a single occasion or drinking heavily and continuously over a number of days or weeks, abstaining and then repeating the cycle. A quantitative definition for binge drinking has been reported in studies from the United States as the consumption of five or more drinks per occasion for men and four or more for women, with one drink being equivalent to 360 ml of beer, 120 ml of wine or one shot (37 ml) of hard liquor.[60,61] In Australian studies, however, binge drinking has been referred to as consuming five or more alcoholic drinks in a row, or even more loosely as consuming large amounts of alcohol on three or four days of the week.[61] The lack of consistent quantitative measures describing binge drinking may contribute to the difficulty in identifying and classifying the type of drinking patterns that dictate alcohol and cardiovascular disease relationships and may account in part for differences in reported findings between studies of alcohol intake and its impact on various cardiovascular outcomes.

McElduff and Dobson found that binge drinkers (in this instance defined as women who consumed five or more drinks on an occasion, or men who consumed nine or more drinks on an occasion) had higher risks for major coronary events than abstainers, even when the overall volume of drinking was low.[63] More recent prospective studies also concluded that heavy drinking episodes increase the risk of coronary heart disease even in light-to-moderate drinkers.[53,64,65] This pattern effect persists after controlling average volume of drinking. Heavier alcohol consumption has detrimental effects on blood pressure and coronary heart disease.[66,67] In the prospective, observational CARDIA study, over 3000 participants between the age of 30 and 45 were followed for 15 years. In this American study population, heavier drinking was associated with a higher incidence of coronary calcifications (again, a surrogate endpoint) after adjustments for potential confounders and intermediary factors.[58] In this study not only high levels of alcohol consumption but also binge drinking was associated with atherosclerosis of the coronary arteries. This association is consistent with previous studies of binge drinking and coronary heart disease events, most of which found higher rates of events among persons who binge.[53,68] So, binge drinking seems to be associated with coronary heart disease by its influence on atherosclerosis, and dysregulation of inflammatory cytokines associated with the hangover after a binge has been suggested to be a possible mechanism.[69,70]

This influence on atherosclerosis also becomes apparent in a study that showed that men with a heavy, acute style of alcohol consumption had a significantly greater four-year progression of carotid atherosclerosis than men with a more evenly distributed drinking pattern.[69] The positive relationship between heavy doses per sitting and carotid atherosclerosis progression was observed for use of both beer and spirits, after adjustment for the total average level of alcohol use. The magnitude of these relationships was largely unaffected by adjustment for baseline atherosclerosis, known risk factors, and medications. The findings were consistent across different measures of atherosclerosis progression, with heavy acute drinking showing progression of maximum and mean intima-media thickness of the carotid artery and increased plaque height. The observed relationships remained, and appeared to be even stronger, in the analysis of the subgroup that was initially free of the diagnosis or signs of prevalent ischaemic heart disease.

Binge drinking has other detrimental cardiovascular effects. In addition to its effect on coronary heart disease, an irregular pattern of heavy drinking appears to have a relationship with other types of cardiovascular death, such as stroke or sudden cardiac death.[71,72] This relationship is consistent with the increased thrombosis[73] and lowered threshold for ventricular fibrillation that occur after heavy drinking.[74,75] Irregular heavy drinkers seem predisposed to structural (i.e., histological) changes in the heart muscle and the adjacent impulse-conducting system, which decreases the threshold for ventricular fibrillation.[76]

Additionally, heavy drinking has been shown to increase low-density lipoproteins, which have been linked to negative cardiovascular outcomes.[46]

In summary, a pattern of irregular heavy drinking is mainly associated with physiological mechanisms that increase the risk of sudden cardiac death and other cardiovascular outcomes, whereas regular low-to-moderate alcohol consumption might be associated with physiological mechanisms linked to favourable cardiac outcomes.[75,77] However, epidemiological studies that have focused on individuals and the consequences of drinking (e.g. cohort and case-control studies) are still scarce, and some of them have found heavy-drinking occasions to have no detrimental effects on morbidity.[66,78]

BINGE DRINKING AND CONFOUNDERS

Even in studies where a drinking pattern has been evaluated carefully, it should be taken into account that there are several potential confounding lifestyle and demographic factors associated with both drinking pattern behaviour and cardiovascular risk that need to be considered. A pattern of binge drinking behaviour may be linked to other 'risk' behaviour with cardiovascular implications, including tobacco smoking or even illicit drug use.[79]

Age, a major atherosclerosis risk factor, has a significant bearing on alcohol drinking patterns. Alvarez and colleagues[80] reported a higher weekend alcohol intake by Spaniards aged 14 to 29 years, while those aged 30 to 59 years had a more regular but higher intake during the rest of the week. Among Australian males aged 18 to 64 years, most drank at responsible levels with the largest proportion (over 90%) of responsible drinking being in those aged 65 years or over. However, males aged 18 to 24 years made up the greatest percentage (14.8%) of those drinking at harmful levels. This is similar to findings in the United States, where frequent heavy drinking comprised 27% of 18- to 29-year-old men, while only a smaller (4%) proportion was found in those 65 years and over.[81]

Gender, another major risk factor for atherosclerosis, is also associated with differences in alcohol drinking patterns. Studies show consistently higher rates of binge drinking among men than women. However, some of these studies used the same definition of binge drinking for both men and women, without accounting for gender differences in the metabolism of ethanol or body mass. The pattern of alcohol consumption varies according to social groups.[80,82] Those who are single, separated or divorced, or living in a shared accommodation, drink more frequently and are more likely to be heavy drinkers (defined as consuming >80 g of alcohol/day, approximately six standard drinks) than those who are married.[83] Those who are unemployed have a higher alcohol intake and a higher frequency of alcohol use than those who studied, worked, performed homemaker duties or were retired.[80] Ragland *et al.*[82] showed that even in high-stress occupations, being married was associated with lower alcohol consumption, possibly protecting against occupational factors that influence alcohol consumption. Alvarez and colleagues[80] found that individuals with a low academic level, which included those with no schooling or who received primary or secondary schooling, drank less frequently but in higher quantities.

Alcoholic beverage preference is also associated with alcohol drinking patterns and represents another potential confounder of interpretation of alcohol and cardiovascular disease relationships.[19] A Spanish study[83] found that in regular drinkers, those aged <39 years, predominantly consumed beer and spirits while those aged ≥40 years favoured wine. Another Spanish study showed that people who consume one type of beverage often drink in low-to-moderate amounts, unlike people drinking all three beverages (beer, wine and spirits), who showed the highest percentage of a heavy drinking pattern.[84] In a Danish study moderate wine drinkers appeared to be at lower risk of becoming heavy and excessive drinkers favouring the health effect of wine over the other types of alcohol.[85] On the other hand, in Australia, young binge-drinking men were almost exclusively beer drinkers while women consumed a much wider variety of beverages including beer, wine and spirits.

CONCLUSIONS

The French paradox illustrates the relationship between lifestyle and cardiovascular risk. It is, however, doubtful whether this paradox still exists for the current French population. According to the 'time-lag hypothesis' modern France does not differ from the rest of the world with regard to the incidence of cardiovascular disorders.[86] The mortality rates in the 1980s, on which the paradox was based, reflect the lifestyle of France in the 1950s and 60s rather than in the 1980s, since it takes decades for atherosclerosis to develop. In the view of the supporters of the paradox the consumption of wine plays a pivotal role influencing the atherothrombotic process. Although it confirms the favourable effect of modest alcohol consumption on cardiovascular risk observed in many epidemiological studies, the superiority of wine over other alcoholic drinks is debatable. Many studies show that wine drinkers tend to have a healthier lifestyle profile than consumers of beer and/or liquor. A large survey in the United States even demonstrated that some or all of the apparent protective effects of moderate alcohol consumption on cardiovascular diseases may be due to residual or unmeasured confounding.[87] Without adequate control for such confounders conclusions are premature

and not justified. The exact clinical significance of other constituents in wine, such as the polyphenols, is not elaborated yet.

In contrast to moderate drinking, there is quite some evidence that incidental heavy or binge drinking is associated with an increased cardiovascular risk. However, for both spectra of consumption only randomised intervention trials with many participants, a long follow-up, and solid study end points might unravel the mysteries of alcohol. Because of ethical and practical objections it is unlikely that such a study will ever be performed. Nevertheless, the message at this stage seems clear: protection or harm is more related to the quantity of alcohol that we consume than to the content of the bottle.

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ORIGINAL ARTICLE

Oscillometric blood pressure measurements: differences between measured and calculated mean arterial pressure

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ABSTRACT

Mean arterial pressure (MAP) is often used as an index of overall blood pressure. In recent years, the use of automated oscillometric blood pressure measurement devices is increasing. These devices directly measure and display MAP; however, MAP is often calculated from systolic blood pressure (SBP) and diastolic blood pressure (DBP) as displayed by the device.

In this study we have analysed measured and calculated MAP, obtained by two different oscillometric BP measurement devices in two different patient cohorts.

The first cohort included 242 healthy subjects (male 40.5%, 50±13 years). BP measurements were performed with a Welch Allyn 5300P device. We found a small but significant difference between measured MAP and calculated MAP (MAP_{m-c}: -1.8 mmHg, range -5.7 to 12.9 mmHg, p<0.001). MAP_{m-c} showed a significant, but weak correlation with DBP and SBP.

The second cohort included 134 patients with glomerular diseases (male 63%, 50±14 years). BP measurements were performed with a Dinamap 487210 device. In this group we also observed a small difference between measured MAP and calculated MAP (+1.7 mmHg, range –15.3 to 28.2 mmHg, p<0.001). MAP_{m-c} correlated with age, all blood pressure indices and heart rate.

An overall analysis showed that age, SBP, DBP, and type of device are all independently related to MAP_{m-c}.

There is a significant difference between measured and calculated MAP. The difference is small on average; however, this MAP_{m-c} can be large in the individual patient. Moreover, there are differences of reported MAP between devices. Our data suggest that calculated and measured MAP cannot be used interchangeably.

KEYWORDS

Blood pressure measurement, mean arterial pressure, oscillometry

INTRODUCTION

Systemic blood pressure (BP) is one of the most important cardiovascular risk factors which is amenable for treatment. Thus far most long-term epidemiological studies have used BP values based upon auscultatory measurement with a mercury sphygmomanometer. With this technique systolic blood pressure (SBP) and diastolic blood pressure (DBP) are defined by the appearance and disappearance, respectively, of sounds over the brachial artery during deflation of the cuff (Korotkoff sounds I and V). Other indices of BP can be derived from SBP and DBP. Pulse pressure (PP) is calculated by SBP – DBP and mean arterial pressure (MAP) is calculated by DBP + 1/3 PP.

There is an ongoing debate on which of the above-mentioned BP parameters is most important in predicting cardiovascular risk and renal outcome.[1-4] Some studies suggest that MAP may be more accurate in predicting cardiovascular prognosis than other BP indices.[1,2]

Both in clinical research and clinical practice, the use of oscillometric BP measurement devices for determining BP is increasing.[5] The oscillometric BP measurement device measures oscillations from the blood vessel wall during cuff deflation. The pressure at which the oscillations are maximal is defined as MAP. The device then calculates the SBP and DBP with an algorithm.[6,7] The MAP measured oscillometry is the most reliable BP index of the oscillometric BP measurement device.[6] Although the measured MAP is reported by most devices,

some researchers do not use it. Instead, they calculate the MAP from the SBP and DBP displayed by the device with the formula DBP + 1/3 PP.[8,9] Of note, some devices do not report MAP.

It is unknown if the measured MAP and calculated MAP are similar. In this study we compared the measured and calculated MAP obtained by two different oscillometric BP measurement devices in two study groups. Our data suggest that measured and calculated MAP cannot be used interchangeably.

METHODS

For this study we used archival BP data obtained with an oscillometric BP measurement device in two different patient cohorts.

Firstly we retrieved recordings of oscillometric BP measurements performed at our research unit in persons who were evaluated in the course of a screening programme for the detection of kidney disease. Participants filled in a questionnaire on medication use. Body weight and height were measured, BMI was calculated. Blood pressure was measured using an automated oscillometric device (Welch Allyn 5300P) while subjects were in a sitting position with the arm supported at heart level. Five BP readings were done at five-minute intervals.

For the second analysis we used BP recordings of patients with kidney disease participating in a research programme on markers of progression of glomerular disease.[10,11] In these patients approximately ten consecutive BP readings were performed at three-minute intervals with an automated device (Dinamap 487210, Critikon Tampa FL). In these patients BP was also measured by an experienced nurse using a sphygmomanometer. This 'office' reading always followed the automated measurement. The use of an ACE inhibitor, β-blocker, diuretic agent or calcium antagonist was recorded.

Calculations

The last three and five BP measurements, respectively, were used for analysis. SBP, DBP and MAP were retrieved from the printed output lists. Calculated MAP was derived from SBP and DBP using the formula DBP + 1/3 PP. PP was calculated by SBP – DBP. In each individual there were three and five pairs of calculated and measured MAP, respectively. To obtain the average difference per subject, the calculated MAPs were subtracted from the measured MAPs and these values were averaged (MAP_{m-c}). For paired comparisons we used the Wilcoxon signed-rank test, for unpaired comparisons we used the Mann-Whitney test. The MAP_{m-c} was correlated with several variables using Spearman's analysis. Multiple logistic regression was used to determine factors independently related to MAP_{m-c}. The analyses were done for the two groups separately. To evaluate the possible effect of the type of device, we also analysed the overall dataset.

All data are presented as means (±SD) or medians (range) when appropriate, All statistics were performed using SPSS software, version 14.0 (Chicago, IL). Differences were considered significant with p value <0.05.

RESULTS

Group 1

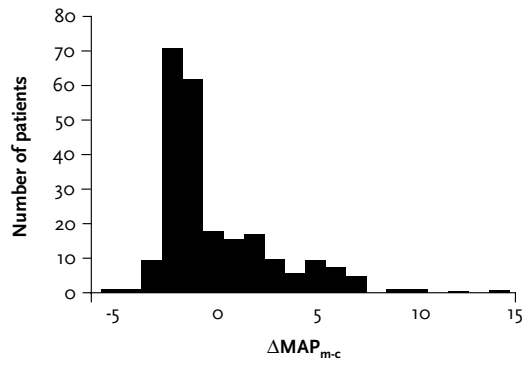
BP readings were available for 242 subjects. Their clinical characteristics are shown in *table 1*. We observed a significant difference between measured MAP and calculated MAP (p<0.001). The nonparametrical distribution of the MAP_{m-c} is shown in *figure 1A*. The median MAP_{m-c} amounted to -1.8 mmHg (p<0.001), but the difference can be large in individuals (range -5.7 to 12.9 mmHg). The MAP_{m-c} was slightly but significantly different in men and women (p=0.008). The median MAP_{m-c} in this group was -2.0 mmHg in male subjects and -1.7 mmHg in female subjects. Correlations of MAP_{m-c}

Table 1. *Baseline characteristics*

	Group 1 (n=242)			Group 2 (n=134)		
Variables	**All**	**Male (n=98)**	**Female (n=144)**	**All**	**Male (n=85)**	**Female (n=49)**
Age (years)	50±13	55±12	47±12	50±14	51±14	50±15
BMI (kg/m²)	25.7±4.7	26.3±3.8	25.3±5.2	27.0±4.7	26.8±4.2	28.2±5.5
Systolic blood pressure (mmHg)	121.8±14.0	126.8±13.8	118.4±13.2	131.9±25.2	132.1±25.6	131.6±24.8
Diastolic blood pressure (mmHg)	74.9±9.7	78.3±9.3	72.6±9.4	79.2±12.2	79.3±12.9	79.2±10.9
Measured mean arterial pressure (mmHg)	90.0±10.5	93.6±10.7	87.6±9.7	98.1±15.9	99.2±16.8	96.2±14.3
Antihypertensive treatment* (%)	16.1	14.3	17.4	86.6	89.4	81.6

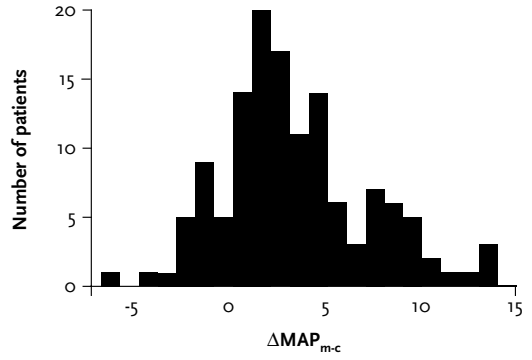
Values are expressed as means ± SD or %. *Antihypertensive treatment: use of calcium entry blockers/ACE inhibitor or angiotensin II receptor blocker/diuretic/β-blocker.

Figure 1A. *Histogram showing the difference between measured and calculated mean arterial pressure in 242 subjects*



Blood pressures recorded with Welch Allyn 5300P oscillometric device. Clearly, distribution of MAP_{m-c} is skewed.

Figure 1B. *Histogram showing the difference between measured and calculated mean arterial pressure in 132 subjects*



Blood pressures recorded with Dinamap 487210 oscillometric device. Of note, two outlaying values (-15.3 and 28.2) are not depicted.

with age, BMI, SBP, DBP, measured MAP, pulse pressure and heart rate are shown in *table 2*. Only DBP and SBP showed a significant, but weak correlation with MAP_{m-c}. In multivariable analysis it appeared that sex was not independently related to MAP_{m-c}. Both SDP and DBP were significantly related to MAP_{m-c}.

Group 2

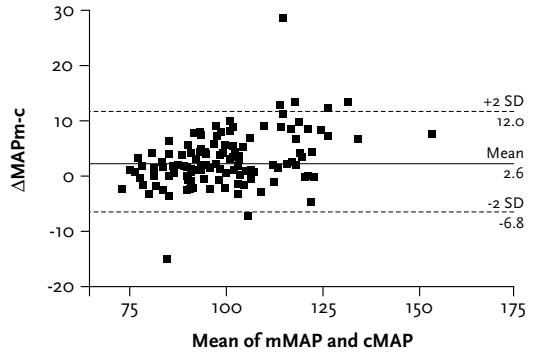
BP readings were available for 134 patients (*table 1*). In this group we also observed a significant difference between measured MAP and calculated MAP (p<0.001), with again a nonparametrical distribution of the MAP_{m-c} (*figure 1B*). The median MAP_{m-c} amounted to +1.67 mmHg (p<0.001), with a large range between individuals (-15.3 to 28.2 mmHg). *Figure 2* describes the relation between MAP_{m-c} and the mean MAP. In this group there was no difference in MAP_{m-c} between male and female subjects. All BP indices and heart rate correlated with MAP_{m-c}, although none of these correlations were very strong (*table 2*). In multivariable analysis only age (p<0.001) was independently related to MAP_{m-c}.

In this second patient group data on auscultatory measurement were available. There was no significant difference between the mean oscillometric SBP and the mean SBP as measured by sphygmanometry (median difference 2.1 mmHg), although the values for the individual patients were highly variable (range -31.6 to + 22.6 mmHg). We did observe a difference between DBP measured by oscillometry and auscultation, respectively, which again was very variable between the individual patients (median -0.6 mmHg, range -21.0 to +16.0 mmHg, p=0.005). When comparing the MAP measured oscillometrically with the MAP calculated by SBP and DBP measured by auscultation, the difference observed was median +1.5 mmHg (range -16.1 to 23.5 mmHg, p=0.05); for MAP calculated by oscillometry *vs* MAP calculated by auscultation, the difference was -0.3 mmHg (range -17.3 to 15.3 mmHg, p=0.04).

Table 2. *Correlations of MAP_{m-c} with patients characteristics*

	Group 1		Group 2	
Variables	**Spearmans rho**	**p value**	**Spearmans rho**	**p value**
Age (years)	-0.10	ns	0.38	<0.01
BMI (kg/m²)	-0.04	ns	0.13	ns
Systolic blood pressure (mmHg)	-0.16	0.01	0.31	<0.01
Diastolic blood pressure (mmHg)	-0.21	<0.01	0.29	<0.01
Measured mean arterial pressure (mmHg)	0.02	ns	0.46	<0.01
Pulse pressure (mmHg)	-0.02	ns	0.34	<0.01
Heart rate (/min)	-0.00	ns	-0.20	0.02

Figure 2. *Bland-Altman plot*



Relation between MAP_{m-c} and the mean of those mean arterial pressures for the second patient group. R=0.35; p=0.01.

Lastly, we performed an analysis of the combined data of the oscillometric BP readings in both groups. In multivariate analysis age, SBP, DBP, and type of device were independently related to MAP_{m-c}.

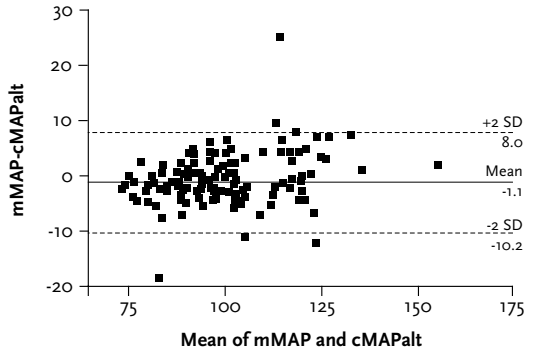
DISCUSSION

We found a small but significant difference between the measured and calculated MAP in oscillometric BP readings. The measured MAP was lower than the calculated MAP in the first cohort, while it was higher than the calculated MAP in the second cohort. The difference between measured and calculated MAP was dependent on age, SBP and DBP. Of note, the observed differences were also clearly dependent on the BP measurement device (Welch Allyn *vs* Dinamap). It has been shown before that although all devices on the market have passed an obligatory test protocol, the accuracy of different devices can vary.[5,12]

Although the differences between measured and calculated MAP seem small, large differences have been observed in individuals. Variability will be even larger when using only one single BP measurement (*table 3*). Therefore, we feel that measured and calculated MAP cannot be used interchangeably. We were unable to find important determinants of the difference between measured and calculated MAP. Although SBP and DBP were related to MAP_{m-c} in group 1, and age and BP in group 2, these factors can only explain the variation in MAP to a limited extent.

Recently, the method of calculating the MAP has been debated. Bos *et al.* showed that the well-known formula of MAP = DBP + 1/3 PP underestimates the 'real' MAP, with larger underestimations at higher pressures.[13] A new formula of DBP + 0.4 PP was suggested and was validated for a large range of BP values.[14] Use of this new formula results in a higher value of the calculated MAP. To determine if the application of this new formula would affect our conclusions, we reanalysed the data of our second patient cohort. In this new analysis the difference between measured and calculated MAP became negative (median -1.6 mmHg, range –18.8 to +24.8 mmHg); however, the difference remained statistically significant (p=0.007). Thus, the use of the new formula does not nullify the difference between calculated and measured MAP in oscillometry (*figure 3*).

Figure 3. *Bland-Altman plot*



Relation between the difference of measured mean arterial pressures (MAPs) and the MAP calculated by the alternative formula (mMAP-cMAPalt) and the mean of those MAPs for the second patient group. r=0.26; p=0.01.

Table 3. *MAP_{m-c} (mmHg) for the consecutive BP measurements*

		MAP_{m-c} 1	MAP_{m-c} 2	MAP_{m-c} 3	MAP_{m-c} 4	MAP_{m-c} 5
Group 1	Mean ±SD	-0.6±3.2	-0.4±3.8	-0.7±5.1	NA	NA
	Median (range)	-1.7 (6-17)	-1.7 (-7-16)	-1.0 (-17-21)	NA	NA
Group 2	Mean ±SD	1.9±6.4	2.5±6.2	2.6±7.4	2.2±5.6	2.4±5.4
	Median (range)	1.7 (-17-24)	1.5 (-18-25)	2.2 (-27-25)	1.0 (-12-18)	2.7 (-12-18)

NA = not available.

To our knowledge only Smulyan *et al.* have evaluated the difference between calculated MAP and measured MAP in oscillometric BP measurement (Colin Medical Instrument device).[15] These authors studied patients who underwent a coronary angiography, and observed a weak correlation between the difference in MAP and age (r=0.32). This finding is similar to our finding in the second group (r=0.38) but not to the first group (r=-0.10). The difference between the findings of Smulyan *et al.* and the findings in our first group might be explained by the difference in population. In Smulyan's study there were more men (50%), the subjects were on average older (mean age 60.4 years) and 85% of the subjects used medication for the treatment of cardiovascular disease, whereas in our first group of 'healthy' persons, this was only 16.1%. Our second group had more men (63%), higher BPs and all subjects were patients with kidney disease, so this population may be more like that of Smulyan, explaining the similarity in outcome.

The oscillometric BP measurement device has been compared with intra-arterial BP measurement and with sphygmomanometer BP readings. Loubser *et al.* compared BPs obtained with oscillometric (Dinamap 1845) and intra-arterial methods in postoperative hypertensive patients.[16] In that study the MAP did not significantly differ between the two methods. In contrary, the SBP was underestimated largely (19 mmHg) by the oscillometric method. In further analysis this appeared to be due to large underestimation in hypertensive patients (SBP >160 mmHg), while in the normotensive range (SBP <140) there was no significant difference. In addition, the DBP was significantly overestimated (6 mmHg) by the oscillometric device and this difference remained fairly constant throughout all pressure ranges. Gorback *et al.* performed a comparable study in anaesthesia patients (oscillometric BP measurement (Dinamap 1846SX) *vs* intra-arterial BP readings).[17] They showed the same tendency to underestimated SBP at higher pressures (-9 mmHg), but they could not confirm the overestimation of the DBP. Both DBP and MAP did not significantly differ between the two measurement methods. However, in individual patients the differences were unpredictable and varied from large overestimation to large underestimation for all BP indices (-34 mmHg to +17 mmHg). This large individual variability (from -30 to 25 mmHg) was also found by Pace and East, who compared oscillometric (Dinamap 845XT) and intra-arterial BP readings in patients who underwent elective surgery.[18] Furthermore, they did not find a significant overall difference in SBP and MAP, but confirmed the overestimation (6 mmHg) of the DBP as found by Loubser.

Comparisons of the standard mercury sphygmomanometer and intra-arterial BP show an underestimation of SBP (6 to 10 mmHg) and an overestimation of DBP (2 to 8 mmHg).[19,20]

In most cardiovascular risk studies a sphygmomanometer was used to assess the risk of BP level. Therefore BPs obtained by oscillometry have been compared with sphygmomanometer BPs. For this purpose the American Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS) have both designed a protocol for the validation of oscillometric BP measurement devices by comparing sphygmomanometer BP with oscillometry BPs. The values of the oscillometric BP readings and of the sphygmomanometer readings are compared for SBP and DBP. The oscillometric device is graded 'A' if the difference in read pressure is smaller than 5 mmHg in 60%, smaller than 10 mmHg in 85% and smaller than 15 mmHg in 95% of the readings.

Clearly, these validation studies are developed with the goal to make sure that an oscillometric BP measuring device displays the same SBP and DBP values as a sphygmomanometer in one individual. This is convenient when using guidelines based on sphygmomanometer readings. However, it cannot be excluded that oscillometry measures a different kind of physiological variable of BP than sphygmomanometers do. Smulyan *et al.* found that MAP obtained by oscillometry correlated better with intra-aortal pressure than other BP indices. If oscillometrically measured BP does mark a different kind of physiological variable, this would be masked by adjusting the algorithms to mimic sphygmomanometer outcome, in order to achieve an 'A' grading in validation.

Researchers using an oscillometric device for obtaining MAP should be aware of the difference in calculated and measured MAP. Therefore, researchers should describe their method of obtaining MAP with an oscillometric device precisely, especially describing the use of measured MAP or calculated MAP.

In this study we have not calculated relative risks for calculated and measured MAP, nor have we compared the oscillometric measurements with sphygmomanometer or intra-arterial BP readings. Therefore, we can not conclude which MAP is the best to use. We did find a relatively large range in the difference between calculated and measured MAP for the individual patient obtained from oscillometric BP measuring. With that finding, we want to emphasise the importance of describing the method of determining MAP when using an oscillometric BP measurement device in research.

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ORIGINAL ARTICLE

Reintroduction of Riva-Rocci measurements to determine systolic blood pressure?

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ABSTRACT

Introduction: In 1896, Riva-Rocci introduced the upper arm cuff to measure systolic blood pressure. In 1905, Nicolai Sergeivich Korotkoff added the auscultatory technique, allowing measurement of both systolic and diastolic blood pressure. Both methods have, to our knowledge, never been formally tested against each other. In this study, we want to fill this gap in history. Methods: We measured systolic blood pressure by the Korotkoff sound technique and approximated the Riva-Rocci technique by measuring cuff pressure at the moment that the first pulsation became visible in Finapres readings, at the finger. This proxy of the Riva-Rocci technique allows an objective, offline, analysis. Measurements were performed simultaneously on the same arm in 57 subjects. Results: Systolic blood pressure measured by the Korotkoff sound technique was 167±30 mmHg (mean ±SD). Systolic blood pressure according to the Riva-Rocci technique was 165±32 mmHg. The Riva-Rocci technique underestimated measurements with the Korotkoff technique by 1.8±4.4 mmHg (NS, p=0.79). Conclusion: Riva-Rocci measurements of systolic blood pressure may be as good as the traditionally used Korotkoff measurements.

KEYWORDS

Blood pressure determination, Korotkoff, Riva-Rocci, systole

INTRODUCTION

In 1896, Scipione Riva-Rocci introduced the upper arm cuff to measure systolic blood pressure (BP) at the upper arm.[1] The radial artery was palpated while the upper arm cuff was inflated. The pressure in a mercury sphygmomanometer, at the moment that the radial artery pulsations disappeared, marked the level of systolic BP. In 1905, Nicolai Sergeivich Korotkoff added the auscultatory technique. Korotkoff described the appearance and disappearance of sounds over the brachial artery, distally of the Riva-Rocci cuff, allowing the measurement of both systolic and diastolic BP.[1] BP measurement with an upper arm cuff in combination with auscultation of sounds, hence known as Riva-Rocci/Korotkoff (RRK) measurements, has become one of the most commonly performed measurements in clinical practice. RRK measurements are the gold standard against which other BP-measuring devices are tested.[2] In the original paper by Korotkoff in 1905, he mentioned that the systolic BP, measured by the appearance of the first sound, is several mmHg higher than the value determined by palpation of the radial pulse.[3] To our knowledge, the Riva-Rocci method and the Korotkoff method, which were introduced before the era of evidence-based medicine, have not been formally tested against each other. In this study we want to fill this gap in history.

In order to compare the two techniques optimally, we approximated Riva-Rocci measurements by recording arterial finger pressure using Finapres.

MATERIALS AND METHODS

Patients

Measurements were performed in 57 healthy elderly subjects and patients with vascular disease and/or hypertension. Twenty-nine of them were women. These subjects were 34 to 83 years of age. Mean height was 1.68±0.10 metres, weight was 82±21 kg. Thirty-nine subjects were on antihypertensive medication at the time

of BP measurement. Three subjects were using nitrates, seven calcium antagonists, 15 ACE inhibitors, 19 β-blockers and 23 were taking diuretics. The subjects had been included in previous studies.[4] We used previously collected BP registrations. These registrations were obtained in studies where BP measurements were performed to rule out pseudohypertension in patients with therapy-resistant hypertension and signs of arteriosclerotic vascular disease (n=13), to validate Finapres BP measurements in an elderly population (n=15) and to study the effects of cuff size on RRK measurements (n=29).[4] The moment of return of flow measurements were performed offline and were done without knowing the RRK values. These studies were approved by the institutional review committees. All participants had given informed consent.

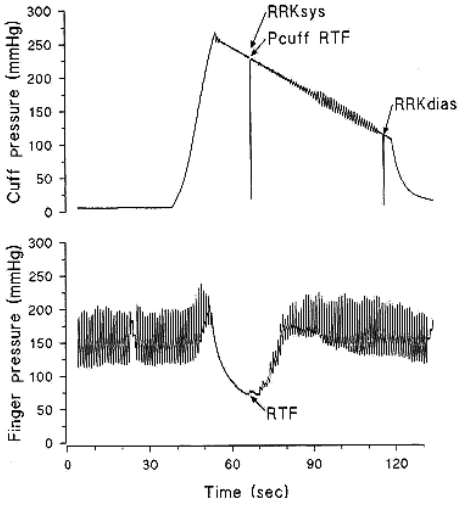
Measurements

Finger pressure (measured with Finapres, TNO model 5, BMI-TNO, Amsterdam, the Netherlands) measurements and RRK measurements were simultaneously performed on the same arm. The RRK measurements were performed by well-trained observers who had recently passed audiographic testing,[5] using a 14 x 38 cm cuff on the dominant arm.

The cuff was inflated rapidly and deflated automatically at a fixed rate of 2.5 mmHg/sec. Cuff pressure was recorded with a strain gauge transducer (Motorola MPX 2050). At Korotkoff phase 1 and 5 a marker was given (*figure 1*).

Riva-Rocci systolic BP was measured offline determining the upper arm cuff pressure (Pcuff) at the moment that the first pulsation became visible at the finger (moment of return to flow, RTF) (*figure 1*).

Figure 1. *Upper panel: Cuff pressure at Korotkoff phase 1 and 5 (RRKsys and RRKdias) and at return to flow at the finger (Pcuff RTF), lower panel: return to flow (RTF) at the finger indicated by Finapres*



Statistical analysis

Data are presented as mean value ± SD. In this analysis we used the average of two measurements in each subject. We compared the two different types of BP measurement using a paired Student's *t* test.

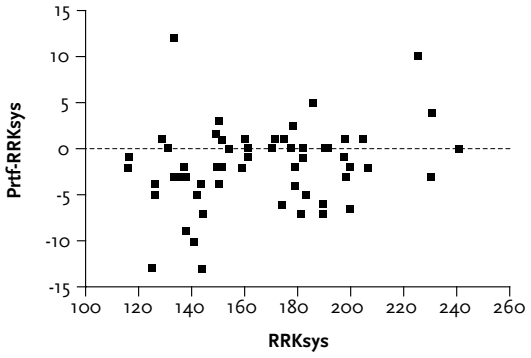
RESULTS

RRK systolic BP was 167±30 mmHg. Heart rate was 67±12 per sec. Pcuff at the time of RTF was 165±32 mmHg. The mean underestimation by Pcuff at RTF compared with RRK systolic BP was 1.85±4.4 mmHg (NS, p=0.79). This underestimation was independent of the RRK systolic BP level. The absolute BP difference between Pcuff at RTF and RRK systolic pressure was 0 to 5 mmHg in 45 subjects, 5 to 10 mmHg in nine subjects and >10 mmHg in three subjects (*figure 2*). There are no significant relationships between the systolic RRK measurements, heart rate and age and Pcuff RTF-RRKsyst. The first Korotkoff sound was noticed at the same time as RTF in 37 subjects, one beat before RTF in eight subjects and two beats before RTF in six subjects. Remarkably, in some subjects the RTF was noticed before the first Korotkoff sound was heard. The RTF was noticed one beat before the first Korotkoff sound was heard in five subjects and six beats before in one subject.

DISCUSSION

Riva-Rocci measurements of the systolic BP did not differ significantly from the Korotkoff measurements. As described by Nicolai Korotkoff himself, Riva-Rocci measurements underestimate Korotkoff measurements.[3]

Figure 2. *Difference between cuff pressure at the moment of return to flow at the finger (Prtf) and the systolic BP measured with the Korotkoff sound technique (RRKsys) in relation to the systolic blood pressure measured according to the RRK technique (RRKsys)*



However, the difference in this study is small (1.85±4.4 mmHg) and nonsignificant. This difference might be explained by the time delay when the pressure wave travels from the upper arm to the periphery. Due to the lower pressure in the arterial system behind the upper arm cuff, the pressure wave propagates more slowly than at normal arterial pressure levels.[6] Since we measured intra-arterial pressure contralaterally in the original study,[4,6] we were able to measure the delay of the pressure wave arriving at the finger of the 'cuff-arm'. At the moment of RTF, this delay was 0.2 to 0.3 seconds. With a cuff deflation rate of 2.5 mmHg/sec, this delay accounts for 0.5 to 0.75 mmHg of the observed average difference of 1.85 mmHg difference. Furthermore, as already suggested by von Recklinghausen, the pressure wave may weaken on its way to the periphery.[7] This explains the delay by one or two beats in eight and six subjects, respectively. On the other hand, we found that RTF preceded the first Korotkoff sound in some subjects. Apparently audible Korotkoff sounds are not always generated at the first passage of a pulse wave.[8] This delay in generation of audible Korotkoff sounds might explain the slight underestimation of systolic RRK measurements when RRK measurements are compared with intra-arterial measurements.[9]

Limitations

The use of finger pressure measurements allowed us to register the pressure distally of the upper arm cuff. This pressure registration at the finger allowed us to make an optimal offline analysis. We were able to register the timing of RTF in relation to the Korotkoff sounds. It is, of course, possible that the finger of a human is less sensitive in detecting minor pressure excursions than finger pressure measurements with Finapres. If this is the case, Riva-Rocci measurements might further underestimate auscultatory measurements. Additional comparisons of RTF measurement, palpatory measurements and auscultatory measurements are needed to settle this issue, and to validate the palpatory Riva-Rocci measurements.

Secondly, our study group is predominately made up of elderly patients with vascular disease and/or hypertension. Therefore, we do not know whether the outcome of this study can be applied to the general population.

We did not follow the British Hypertension Society (BHS) protocol for validation of blood pressure measuring devices.[10] This protocol was developed to compare a device to be tested with RRK measurements. In order to be able to use measurements on the same arm, the protocol prescribes sequential measurements of the device and RRK measurements, since the device measurements and the RRK measurements cannot be performed at the same time on the same arm. The trade-off for using same arm measurements is the introduction of small errors due to spontaneous blood pressure variability. In our study we compare Korotkoff measurements with a proxy of Riva-Rocci measurements. In this case simultaneous performance of both measurements is possible. Since simultaneous comparisons are by nature superior to comparisons of sequential measurements, we felt justified not to follow the BHS protocol.

CONCLUSION

Riva-Rocci introduced the upper arm cuff and the palpatory technique to measure systolic blood pressure 112 years ago. Korotkoff added the auscultatory technique, allowing measurement of systolic and diastolic pressure. Nowadays, more emphasis is placed on the treatment of systolic, rather than on diastolic blood pressure in the management of cardiovascular disease. We therefore re-evaluated the potential value of systolic blood pressure measurements by the Riva-Rocci technique. We want to stress that studying the measurement of systolic pressure by no means means that we consider measurement of the diastolic pressure irrelevant.

One hundred and three years after Korotkoff introduced the auscultatory technique, we have shown that Riva-Rocci and Korotkoff measurements of systolic blood pressure agree well. In doing so, we fill a gap in history. Riva-Rocci measurements of systolic blood pressure might therefore not only be a relic of the past, but also an accurate substitute for Korotkoff measurements.

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ORIGINAL ARTICLE

Thyroid function in patients with proteinuria

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ABSTRACT

Background: Patients with proteinuria may suffer from substantial losses of functional proteins such as hormones and hormone-binding proteins. A limited number of studies have reported urinary losses of thyroid hormones and thyroxin-binding globulin. Overt hypothyroidism attributable to these urinary losses has been described. However, the impact of proteinuria on thyroid function parameters has not been studied in a large patient cohort.
Methods: We evaluated thyroid function parameters in patients with proteinurea who are negative to thyroxine peroxidase antibodies (TPOAbs). Values of free thyroxin and thyroid-stimulating hormone (TSH) were compared with data from age- and gender-matched controls derived from the Nijmegen Biomedical Study, a population-based survey conducted in our hospital.
Results: We evaluated 159 patients. There were 111 males and 48 females. Median (IQR) age was 52 (40 to 62) years, serum creatinine concentration 99 (82 to 134) μmol/l, serum albumin concentration 29 (22 to 35) g/l, and proteinuria 6.6 (3.1 to 10.9) g/10 mmol creatinine. Median TSH was significantly higher in the patients than the controls (1.81 mU/l *vs* 1.34 mU/l, p<0.0001). In the patients, TSH was negatively correlated with serum albumin (r=-0.21; p<0.01). Subclinical hypothyroidism was six times more frequent in the patients (11.3 *vs* 1.8%, p<0.001); however, overt hypothyroidism was observed in only one patient.
Conclusion: Patients with proteinuria have higher TSH levels, consistent with urinary loss of thyroid hormones. However, these urinary losses do not result in overt, clinically relevant, hypothyroidism. The role of subclinical hypothyroidism in these patients needs further evaluation.

KEYWORDS

Hypothyroidism, proteinuria, thyroid hormones

INTRODUCTION

Proteinuria is a hallmark of renal diseases. Severe proteinuria results in the nephrotic syndrome, which is characterised by proteinuria, hypoalbuminaemia, oedema and hyperlipidaemia. Albumin is the most abundant protein in serum and urine. In patients with a nephrotic syndrome urinary losses of albumin are not fully compensated by the increased hepatic production, with hypoalbuminaemia as a consequence. In patients with proteinuria many other proteins beside albumin are lost in the urine. Among these are hormones and hormone-binding proteins. Several studies have documented urinary loss of thyroid hormones and thyroxin-binding globulin (TBG) in patients with proteinuria.[1-4] The clinical relevance of this is unknown. The abovementioned studies included a limited number of patients (in total 49 patients in four studies). In one study overt hypothyroidism was noted in two patients that resolved after remission of the nephrotic syndrome.[3]
In patients with the nephrotic syndrome, loss of thyroid hormones may lead to low free thyroid hormone levels unless production is increased under the influence of thyroid-stimulating hormone (TSH). Furthermore, loss of albumin and TBG may reduce the binding capacity for thyroid hormones, resulting in a decrease in total triiodothyronine (T3) and thyroxin (T4) concentrations.
Thus far no study has systematically evaluated thyroid hormone status in patients with proteinuria. We have analysed thyroid function in a large cohort of patients with proteinuria.
For comparison we have used data obtained in the Nijmegen Biomedical Study, a population-based study in our hospital.[5]

SUBJECTS AND METHODS

In our centre patients with proteinuria are evaluated using a standard protocol.[6] In brief, patients are seen after an overnight fast. Blood pressure and bodyweight are measured and serum and urine samples are collected

for measurement of creatinine and albumin. In addition aliquots of serum are stored at -70°C.
For the current study we thawed frozen samples obtained from 200 consecutive patients studied in the period 2001-2004.

Laboratory methods

In the serum of the patients, TSH, T4, free thyroxin (FT4), T3 and thyroxine peroxidase antibodies (TPOAbs) were measured. TSH, FT4 and TPOAbs were measured as described.[5] For the measurement of FT4 an incubation buffer was used without a physiological concentration of chloride. Since chloride primarily affects T4 binding to albumin, a slight artefact (a decrease of 10 g/l in serum albumin causes apparent increase of FT4 by about 0.5 pmol/l) results that is normally negligible, but must be taken into account with moderate to severe hypoalbuminaemia. To correct for this *in vitro* artefact we used the following formula: corrected FT4 = FT4 + (0.0542 x (serum albumin - 46). Total T4 and T3 were measured by means of a Luminometric immunoassay performed on an Architect immunoanalyser (Abbott Diagnostics, Amstelveen, the Netherlands). Within- and between-assay CVs were: for T4 3.8 and 6.5% at a level of 46 nmol/l, 3.6 and 5.1% at 108 nmol/l and 4.2 and 10.8 at 194 nmol/l respectively; for T3 3.5 and 5.4% at 1.05 nmol/l, 2.8 and 4.3% at 1.68 nmol/l and 2.5 and 3.3% at 6.0 nmol/l. The reference range for T4 is 55 to 155 nmol/l and for T3 1.2 to 2.9 nmol/l. For TPOAbs we used a cut-off value of <12 kU/l to define TPOAbs-negative patients as described.[5] Serum and urine creatinine, and albumin, were measured by standard techniques.[6]

Data analysis

Data of the patients were compared with data from an age- and sex-matched control group derived from the Nijmegen Biomedical Study. The Nijmegen Biomedical Study (NBS) is a population-based survey conducted by the Department of Epidemiology and Biostatistics and the Department of Clinical Chemistry of the Radboud University Nijmegen Medical Centre. A total of 21,757 age and sex stratified randomly selected inhabitants of the municipality of Nijmegen received an invitation to fill out a postal questionnaire on lifestyle and medical history, and to donate an 8.5 ml blood sample in a serum separator tube and a 10 ml ethylenediaminetetraacetic acid (EDTA) blood sample. The response to the questionnaire was 43% (n=9371). Of the responders, 69% (n=6473) donated blood samples.[5] In these blood samples FT4 and TSH were measured.
For the present study matched controls were selected from the NBS database, in a ratio of one (patient) to five (controls) using age and gender as matching criterion.
Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease (MDRD) formula.[7] We used the original formula eGFR(ml/min/1,73 m^2) = 170 x (serum creatinine x 0.0113)$^{-0.999}$ x (age)$^{-0.176}$ x (serum urea x 2.8)$^{-0.170}$ x (serum albumin/10)$^{+0.318}$ x 0.762 (if female) x 1.18 (if black), where serum creatinine in µmol/l, serum urea in mmol/l and serum albumin in g/l.
Statistical analysis was performed using the Mann-Whitney U test for comparison between patients and controls. Pearson's correlation coefficient was used as a parameter for correlation between thyroid parameters and serum albumin concentration or eGFR. For TSH log transformed values were used because of the skewed distribution. P values <0.05 were considered statistically significant.

RESULTS

We studied 200 patients with a renal disease and proteinuria. For comparison we selected 1000 age- and gender-matched controls. Sera of 41 patients and 100 controls were positive for TPOAbs. In view of the well-known relationship between positive anti-TPOAbs and hypothyroidism, we have limited the analysis to TPOAbs-negative patients and controls. Clinical characteristics are presented in *table 1*. Proteinuria values in our patients were 6.6 (3.1-10.9) g/10 mmol creatinine. Overall TSH was significantly higher in the patients. There were no differences in FT4 values. In the patients total T4 concentration was 90 (IQR 78-103) nmol/l and total T3 concentration 1.99 (IQR 1.72-2.27) nmol/l. These parameters were not measured in our matched

Table 1. *Baseline characteristics and thyroid hormone status of patients and controls*

	Proteinuria	Proteinuria *vs* control	Control
Age (years)	52 (40-64)		52 (40-64)
Sex (male/ female)	111/48		642/258
Albumin (g/l)	29 (22-35)	p<0.0001	46 (44-48)
Creatinine (µmol/l)	99 (82-134)	p<0.0001	83 (76-92)
TSH (mU/l)	1.81 (1.04-2.81)	p<0.0001	1.34 (0.98-1.87)
FT4 (pmol/l)	13.1 (11.4-14.8)		13.1 (11.9-14.5)
Anti-TPO (mU/l)	5.7 (4.2-7.8)	p<0.01	5.1 (4.3-6.1)
Overt hyperthyroidism	0 (0%)		2 (0.2%)
Subclinical hyperthyroidism	1 (0.6%)		0 (0%)
Euthyroid	133 (83.6%)		877 (97.4%)
Overt hypothyroidism	1 (0.6%)		0 (0%)
Subclinical hypothyroidism	18 (11.3%)	p<0.001	16 (1.8%)
Undefined	6 (3.8%)		5 (0.6%)

Data are for TPOAbs-negative subjects. Values are given as median (IQR). Hyperthyroidism was classified as overt if TSH was <0.1 mU/l and FT4 >22 pmol/l and as subclinical if TSH was <0.1 mU/l and FT4 ≤22 pmol/l. Hypothyroidism was classified as overt if TSH was >4 mU/l and FT4 <8.0 pmol/l and as subclinical if TSH was >4 mU/l and FT4 ≥8 pmol/l. Definitions according to Hoogendoorn *et al.*[5]

control population of the Nijmegen Biomedical Study. For comparison, normal values as used in our laboratory are 55 to 155 nmol/l for total T4 and 1.2 to 2.9 nmol/l for total T3. Subclinical hypothyroidism was six times more frequent in the patients than in the controls (*table 1*). Of note, overt hypothyroidism was observed in only one patient.

In the patients TSH was negatively correlated with serum albumin (r=-0.21; p<0.001; *figure 1*). TSH was not correlated with eGFR (r=0.05). Total T4 correlated with eGFR (r=0.16, p<0.05), not with serum albumin concentration (r=0.125). FT4 did not correlate with eGFR (r=-0.09). We observed significant correlations between T3 and eGFR (r=0.26; p<0.01) and T3 and serum albumin (r=0.36; p<0.001).

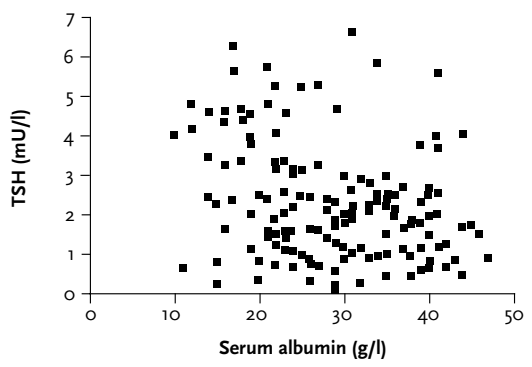
DISCUSSION

Our study demonstrates that abnormalities in thyroid function occur in patients with proteinuria. Specifically, TSH levels were higher in patients with proteinuric renal diseases when compared with age- and sex-matched controls. These data are consistent with the reports of urinary losses of thyroid hormones in patients with proteinuria.[1-4] Apparently, these urinary losses of thyroid hormones in patients with proteinuria result in a stimulation of TSH production. The role of proteinuria is confirmed by the significant and negative correlation between TSH and serum albumin.

Although one study described the development of overt hypothyroidism in patients with a nephrotic syndrome, the prevalence of this complication has remained unclear.[3]

Subclinical hypothyroidism occurred more frequently in our patients and we observed overt hypothyroidism in only one of 159 patients. *Figure 1* clearly illustrates that even in patients with the most severe nephrotic syndrome, TSH levels did not often exceed 4 mU/l.

Figure 1. *Correlation of thyroid-stimulating hormone and serum albumin concentration in patients with proteinuria*



Only patients without anti-TPO antibodies were included in this analysis (r=-0.21; p=0.01).

We noted a correlation between total T4 and T3 and eGFR. In a recent study Lo *et al*. evaluated thyroid function in relation to renal insufficiency.[8] These authors noted an increased prevalence of hypothyroidism, as defined by increased TSH levels, in patients with decreased GFR. Unfortunately, FT4 and proteinuria were not measured by Lo and colleagues. Our data suggest that both proteinuria and GFR influence the activity of the pituitary-thyroid axis. Proteinuria results in loss of thyroid hormones, most probably caused by loss of thyroxin-binding globulin, thus stimulating TSH production.

In view of the well-known relation between TPOAbs and hypothyroidism, we excluded TPOAbs-positive patients and controls from the final data analysis. However, even when considering all patients, overt hypothyroidism was observed in only one patient. The prevalence of TPOAbs positivity was similar in patients and controls. There is one caveat. Since TPOAbs could have been lost in the urine, the usual criteria for discerning between TPOAbs-positive and -negative persons might not fully apply to patients with proteinuria. Of note, there was no correlation between TPOAbs titre and serum albumin.

CONCLUSION

Our study shows that TSH is elevated in patients with proteinuria. However, the clinical relevance of this finding is limited since overt hypothyroidism was present in less than 1% of the patients.

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CASE REPORT

Intestinal ischaemia caused by mesenteric inflammatory veno-occlusive disease

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ABSTRACT

Mesenteric inflammatory veno-occlusive disease (MIVOD) is a rare cause of intestinal ischaemia. Previously described cases of MIVOD demonstrate vasculitis in mesenteric veins with thrombotic occlusion. It is important to distinguish MIVOD from other diseases, such as mesenteric venous thrombosis and systemic diseases. We present a case of a 39-year-old Turkish male in whom MIVOD was diagnosed after exclusion of other causes of ischaemic enteritis.

KEYWORDS

Intestinal ischaemia, thrombosis, vasculitis

INTRODUCTION

Mesenteric inflammatory veno-occlusive disease (MIVOD) as a cause of intestinal ischaemia was first described by Flaherty *et al*. in 1994.[1] They described seven patients who presented with signs of intestinal ischaemia requiring surgical intervention. In each case, the resected colon, small bowel, or both showed venulitis affecting veins of the bowel and mesentery, resulting in thrombotic occlusion of these veins. Vasculitis occurred without involvement of the mesenteric arteries and in the absence of systemic vasculitis or primary intestinal disease. The incidence and aetiology of MIVOD remain unclear because only a few cases have been reported so far. We describe a case of a Turkish male who presented with signs of intestinal ischaemia and required surgical intervention; the diagnosis of MIVOD was made after histopathological investigation of the resected bowel.

CASE REPORT

A 39-year-old Turkish male presented to the emergency room with a six-day history of constipation and progressive epigastric pain, nausea and anorexia for the last four days. Besides urinary stones, his medical history was unremarkable; he was not on any medication. Physical examination revealed a blood pressure of 126/79 mmHg, a pulse rate of 88 beats/min and a body temperature of 38.2 °C. The abdomen demonstrated epigastric tenderness without peritoneal signs. Laboratory findings showed an increased erythrocyte sedimentation rate (40 mm/h), a leucocyte count of 10.2 x 10^9/l and elevated C-reactive protein (231 mg/l). Liver and pancreas enzymes were within normal ranges. An abdominal ultrasound showed ascites, predominantly around the liver. A chest X-ray showed no signs of perforation and an abdominal X-ray excluded bowel distension. The patient developed increasing abdominal pain and subsequently peritoneal signs. An exploratory laparotomy followed, which demonstrated a segment of oedematous, ischaemic ileum; 52 cm was resected. Macroscopic examination of the resected necrotic ileum showed areas of haemorrhage. Microscopic examination revealed haemorrhagic mesenterial fat and necrosis without ulceration. No evidence for Behçet's or Crohn's disease was found. The associated small and medium-sized mesenteric veins showed necrotising vasculitis with occlusive thrombi with a focal marginalisation of granulocytes and deposition of fibrin within the vessel wall (*figures 1* and *2*). Neither arterial involvement nor granulomas were seen. These histopathological findings fit the diagnosis of ischaemic enteritis based on a veno-occlusive mesenteric vasculitis. Blood tests for hypercoagulability and systemic vasculitis were negative. The patient recovered completely with no recurrence in a follow-up period of more than 15 months.

Figure 1. *Veno-occlusive example: focal thrombosis of a middle sized mesenterial vein (20x)*

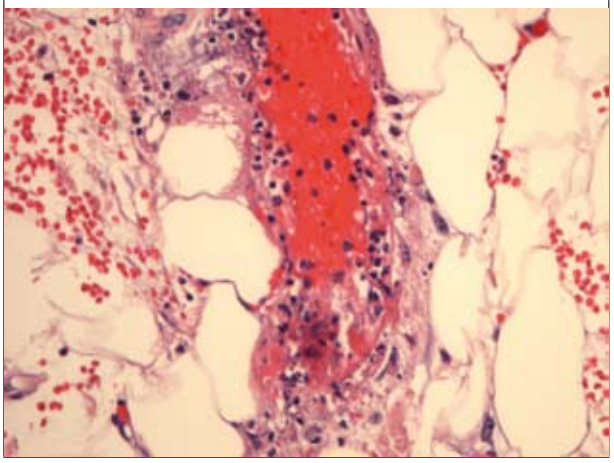
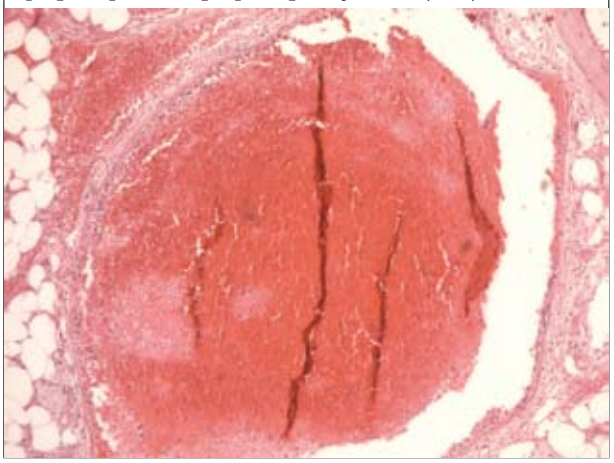


Figure 2. *Small mesenterial vein with necrotising venulitis characterised by destruction of the vessel wall with fibrinoid necrosis and an infiltrate of lymphocytes and polymorph infiltrate (20x)*



DISCUSSION

We present a patient who developed peritoneal signs leading to laparotomy. After small bowel resection, an ischaemic ileum due to MIVOD was diagnosed. Histopathological findings of the resected material revealed an isolated vasculitis of the small mesenteric veins and their intramural tributaries with thrombosis as a secondary manifestation. No arterial involvement was seen. Our histopathological findings are in agreement with previous reports on MIVOD. For example, Tempia-Caliera *et al.* described thrombophlebitis of small veins in the proximal ascending colon with fibroblastic organisation without arterial involvement.[2] Furthermore, Hu *et al.* demonstrated mesenteric oedema and haemorrhage, haemorrhagic infarctions and necrotising venulitis in the submucosa and mesentery with thrombotic occlusions of recent onset.[3] The diagnosis of MIVOD in our case was based on histopathological findings, in combination with the exclusion of other diseases. Intestinal vasculitis mostly occurs secondary to systemic vasculitis, as in Buerger's disease, Behçet's disease, rheumatoid arthritis and systemic lupus erythematosus (SLE) or in association with primary intestinal diseases such as Crohn's disease (*table 1*). However, unlike MIVOD, the systemic vasculitis will predominantly affect the arteries. Furthermore, our patient had no extra-intestinal signs of a systemic disease and no history of bowel disease. Finally, associations with mesenteric venous thrombosis such as a hypercoagulable state, trauma or sepsis were not present in our patient.

A few prior cases with similar presentation and histopathology findings have been reported in literature.[3,4] The disease clinically presents as an ischaemic colitis with abdominal pain for days or weeks accompanied with nausea and bloody stools. Characteristic features of MIVOD are lymphocytic, necrotising, granulomatous or mixed inflammatory infiltrates of the mesenteric veins and its intramural tributaries with secondary development of thrombosis as an important and immediate cause of ischaemic intestinal damage. Some cases describe myointimal hyperplasia associated with chronic MIVOD. No involvement of arterial inflammation or occlusion has been described. The aetiology of MIVOD remains unclear but associations with the antiphospholipid syndrome and the drug rutoside, an antioxidant drug used to treat varicose veins, have been described.[5,6] MIVOD seems to predominantly affect the colon, although it has also been reported to affect the small bowel, omentum and gallbladder.

Treatment of MIVOD involves surgical intervention, as described in previously published case reports. MIVOD is difficult to diagnose in an early stage due to the nonspecific symptoms and the histopathological requirements. Therefore, excluding other diseases using laboratory and radiology findings, such as mesenteric venous thrombosis

Table 1. *Major causes leading to arterial and venous ischemia of the bowel*

Arterial ischemia
Superior mesenteric artery embolism
Superior mesenteric artery thrombosis
Vasculitis (Behcet's disease, SLE, in association with Crohn's disease)
Shock
Venous ischemia
Mesenteric venous thrombosis (hypercoagulable state, trauma, sepsis)
Mesenteric inflammatory veno-occlusive disease

(MVT) and systemic diseases such as Behcet's disease and SLE, becomes of crucial importance. The latter diseases would require therapies such as corticosteroids, immunosuppressive therapy, or anticoagulant therapy. All of these therapies come with a significant risk of side effects.

Follow-up of MIVOD has been reported for up to 15 years in literature. Although recurrence of MIVOD is unusual after surgical resection, it has been described in one case.[2] Maintenance therapy is not required since the prognosis of MIVOD is excellent and the disease is unlikely to reoccur. Our patient recovered completely with no recurrence in a follow-up period of more than 15 months. In conclusion, we present a case of mesenteric inflammatory veno-occlusive disease leading to intestinal ischaemia. This diagnosis should be considered after exclusion of other causes of ischaemic enteritis.

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CASE REPORT

Anakinra suppresses familial Mediterranean fever crises in a colchicine-resistant patient

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ABSTRACT

We describe a 34-year-old male patient suffering from familial Mediterranean fever and experiencing an increase in both the frequency and severity of disease attacks, suggesting resistance to chronic treatment with colchicine. Since no alternative treatment is established, anakinra, an interleukin-1 receptor antagonist, was administered, not daily, as it has been previously reported, but only during crises, with successful outcome.

KEYWORDS

Anakinra, familial Mediterranean fever, interleukin-1 receptor antagonist

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease which mainly affects Armenians, non-Eshkenazi Jews, Turks and Arabs.[1] It has been also reported in other populations of the Mediterranean basin.[2] Due to the increasing number of immigrants from these countries, FMF should not be considered a rare disease throughout Europe. FMF is caused by mutations in the *MEFV* gene on chromosome 16p13.3 which encodes the protein pyrin/marenostrin, a protein which is expressed in the cytoplasm of mature neutrophils and monocytes.[3,4] The disorder is characterised by periodic episodes of fever, peritonitis, arthritis and erysipelatoid erythema and may be complicated by secondary amyloidosis. Colchicine is the recommended treatment as it has shown efficacy in the prevention of both acute attacks and secondary amyloidosis with a nonresponse rate of 5 to 10%.[5] In cases of colchicine resistance or intolerance, other medications, as the interferon-alpha, thalidomide, prazosin and etanercept, have shown efficacy, resolving the attack symptoms or even improving the symptoms of amyloidosis.[6-9] Anakinra, a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra), has been reported to be successful in everyday use, affecting both the severity and the frequency of FMF attacks.[10-13] Nevertheless, its favourable effect when administered only during crisis needs elucidation. Here, we report the effectiveness of anakinra in the remission of FMF attacks in a patient resistant to colchicine.

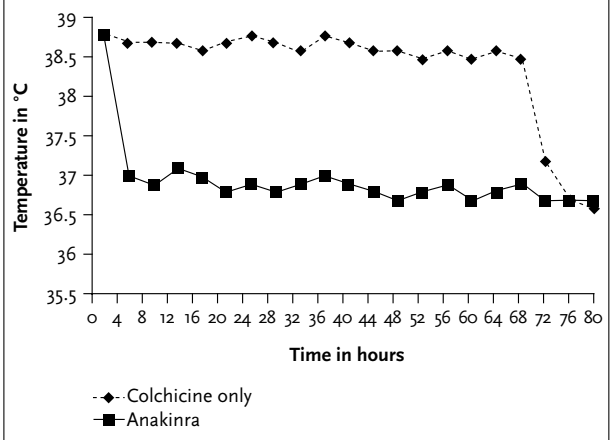
CASE REPORT

A 34-year-old male FMF patient, homozygous for pyrin M694V mutation,[2] was referred for signs attributed to colchicine resistance after several years of successful treatment. He reported more frequent attacks (ten episodes during the last year) characterised by more severe symptoms (worsening of the abdominal pain), despite being on treatment with colchicine at a high dose (2.5 mg). Each crisis lasted 70 to 72 hours and the abdominal pain, which was the initiating symptom, was accompanied by high fever (38.5 to 39°C) shortly afterwards. His renal function was normal, proteinuria was absent and there were no signs of organomegaly. His medical record was insignificant for arthritis or pleuritis. C-reactive protein (CRP) levels of >25 mg/dl (normal 0-0.5) and elevated white blood cell counts were repetitively measured during previous crises. As he experienced a severe impairment in his quality of life, and being aware of the reported efficacy of anakinra in the treatment of FMF patients resistant to colchicine, he asked to be given anakinra, as an additional treatment to colchicine. It was proposed to administer anakinra (Kineret, Amgen, USA) subcutaneously at a dose of 100 mg immediately after the onset of the abdominal pain, which was the initiating

symptom of the attack. Anakinra would be repeated after 24 hours according to the clinical course. No other medication which could affect the clinical course, such as analgesics or anti-inflammatory drugs, was recommended during the episodes. Colchicine was never withdrawn for reasons of secondary amyloidosis prevention and its dose was not altered. The overall procedure was approved by the Institutional First Internal Medicine Department Board and an informed consent was obtained from the patient.

The benefits of anakinra pulses were observed in the following six-month period. The patient reported only three minor episodes of FMF, with significant amelioration in the abdominal pain after the immediate use of anakinra according to the protocol described. His body temperature returned to normal values within an hour (*figure 1*). The only remaining symptom was a mild abdominal discomfort lasting for about 48 hours, which did not affect his daily or occupational activities. In two episodes, where the protocol was followed *lege artis*, the patient experienced immediate and lasting relief with a single dose of anakinra, given within 30 minutes of the onset of the episode, with no need for further palliative measures. Controversially, a single episode of inevitable deviation from the therapeutic protocol, a five-hour delay in the administration of anakinra, substantially decreased the efficacy of the regimen. Although this late first dose immediately relieved the febrile attack, a second 100 mg dose was repeated 18 hours later since a more severe abdominal discomfort (without fever) appeared. This second dose immediately cured the patient's crisis. As he was treated as an outpatient, we did not have the opportunity for a close laboratory follow-up.

Figure 1. *Representative pattern of fever during FMF attacks, before (dot line) and after (solid line) the introduction of anakinra in the patient, suggesting immediate response to anakinra*



The dotted line, representing crisis under colchicine monotherapy, is based on evaluation of patient's own observations. 0 denotes onset of symptoms.

CRP values were only available during the first episode, in particular 20 hours after the anakinra administration when the symptoms had already resolved. Thus, CRP was found to be significantly diminished (2.2 mg/dl) compared with available values observed during his previous FMF attacks (>25 mg/dl). No adverse reactions were observed. The benefit of anakinra introduction in FMF crisis is schematically represented in *figure 1*. There is also evidence that the frequency of the attacks after the introduction of anakinra (three crises over six months, mean 0.5) might have been reduced, when compared with the situation in the previous year (ten crises over 12 months, mean 0.9). However, if we combine both the frequency and severity of crises before and after the introduction of anakinra by scoring arbitrarily 2 for each month with a severe crisis, 1 for each month with a mild crisis and 0 for each month with no crisis and using Wilcoxon's test for unpaired samples, a statistically significant difference at $p<0.01$ is observed ($T1 = 87$, $T2 = 84$).

DISCUSSION

Our case report indicates that anakinra provides significant clinical benefit in the treatment of FMF attacks in nonresponders to colchicine. The initial concept was motivated by both previously published reports suggesting the efficacy of anakinra as a continuous daily medication and the patient's insistence, who, being a medical doctor himself, was desperately seeking an alternative treatment, as he experienced a continuous impoverishment of his quality of life. In fact, the patient himself insisted on the use of anakinra. Nevertheless, the administration protocol was proposed by our team. Anakinra was not used as a daily treatment, as it has been previously reported, but only during the episodes of the disease. This was repeated at three consecutive crises. Anakinra showed efficacy in all cases, especially when administered early.

Anakinra competitively inhibits IL-1 binding to the IL-1 receptor type 1 (IL-1RI) in a way that mimics the activity of endogenous IL-1Ra. This implies that even though recombinant IL-1Ra binds to IL-1RI with nearly the same affinity compared with IL-1, a 10- to 100-fold greater IL-1Ra molecular load is needed for the inhibition of IL-1 activity.[14] Taking this into consideration, we may hypothesise that the time-related efficacy of anakinra, which suggests a crucial role of IL-1β inhibition in the onset of the FMF inflammatory process, might be explained by the different IL-1β 'load' or, furthermore, by the different levels of inhibitors other than anakinra involved in the cytokine pathway. Based on this experience, we underline the necessity for the immediate administration of anakinra, as close to the initiation of symptoms as possible. However, generalised speculations can not be made from a single case.

Concerning autoinflammatory syndromes, anakinra has previously shown significant effectiveness in familial cold inflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological cutaneous articular syndrome.[15,16] These related disorders are associated with heterozygous mutations in the *CIAS1* gene, which encodes the protein cryopyrin, a pyrin-like protein that plays an essential role in the regulation of IL-1β secretion through caspase-1 activation, sharing common characteristics with FMF.[17]

The exact function of pyrin, which plays a key role in FMF, is not well established. However, a negative regulatory role in the caspase-1 dependent production of IL-1β has been proposed, either through interaction of its N-terminal domain with ASC[4] or through inhibition of caspase-1 catalytic domains after the binding of pyrin β30.2 domain.[10] Consequently, the use of an IL-1β antagonist could be a rational choice in the treatment of FMF. Furthermore, there is no alternative to colchicine with established efficacy, thus urging for new medications for patients who have developed resistance or intolerance to colchicine. As a result, anakinra has been used in the treatment of such patients as a daily medication with significant reduction in both severity and frequency of the FMF attacks,[10-13] while the levels of amyloid and acute phase reactants were controlled.[10] Moreover, the fever attacks reappeared as soon as the drug was discontinued, enhancing the evidence of its efficacy.[10,11,13]

CONCLUSIONS

This case suggests that the addition of anakinra could be a potentially useful alternative therapeutic approach for FMF attacks in patients not responding to colchicine alone. The elevated cost of anakinra is moderated by its occasional use during crisis. As no alternative solution is established, treatment with anakinra could ameliorate the quality of life in patients resistant to colchicine. On-demand use of anakinra is suggested as soon as the first symptoms occur, with a second dose repeated 24 hours later if necessary without discontinuing colchicine. However, more longitudinal studies are needed to elucidate the clinical outcome and the short- and long-term efficacy of the on-demand anakinra use in FMF patients.

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Netherlands
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PHOTO QUIZ

Endoscopy for obstructive jaundice

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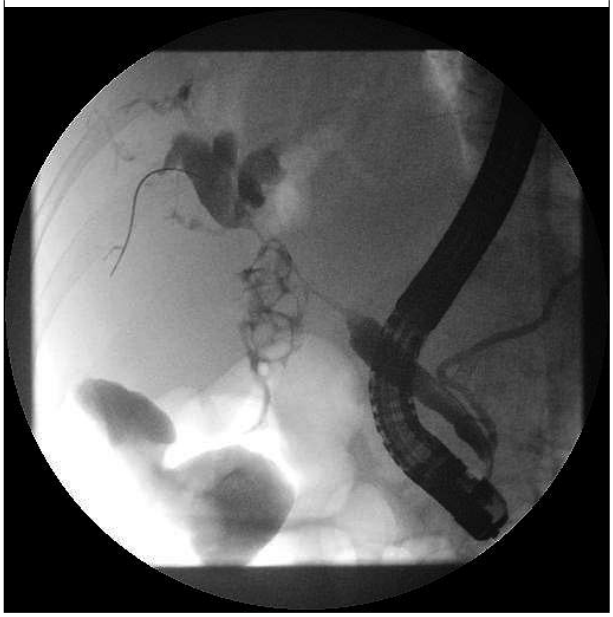
CASE REPORT

A 76-year-old woman was referred for obstructive jaundice. Her medical history was unremarkable, apart from hypertension and type 2 diabetes mellitus. Recently, she observed mild yellowing of her eyes and skin. She had no further complaints, besides vague upper abdominal discomfort and some weight loss during the past months. Apart from jaundice, physical examination was unremarkable. Laboratory results showed an iron deficiency anaemia and cholestatic liver function tests. Endoscopic retrograde cholangiopancreaticography (ERCP) was performed (*figure 1*).

Figure 1. *Endoscopic retrograde cholangiopancreaticography with a guidewire in the hepatocholedochal duct*



WHAT IS YOUR DIAGNOSIS AND HOW TO PROVE IT?

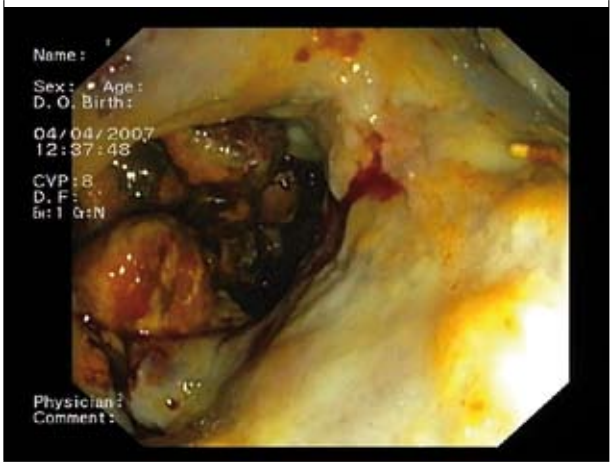
See page 493 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (ON PAGE 492)
ENDOSCOPY FOR OBSTRUCTIVE JAUNDICE

DIAGNOSIS

ERCP showed aerobilia, dilated intrahepatic biliary ducts and a long stenotic segment of the hepatocholedochal duct. The gallbladder is filled with stones. Contrast in the colon is observed, therefore a cholecystocolonic fistula was suspected. A colonoscopy was performed and a tumour was seen at the hepatic flexure. Within the tumour a cavity filled with gallstones could be reached (*figure 2*). Biopsies showed intestinal type adenocarcinoma.

Figure 2. *Colonoscopy showing a tumour at the hepatic flexure with a cavity filled with gallstones*



Immunohistological staining suggested a primary gallbladder carcinoma. Curative resection of the tumour was impossible and a palliative colocolostomy and hepatico-jejunostomy was performed. Unfortunately, nine days after surgery the patient died of an abdominal sepsis.

Gallbladder carcinoma is associated with a poor prognosis and a cholecystocolonic fistula demonstrates advanced disease. Curative resection, however, is still possible in the absence of extended hepatic and biliary involvement.[1,2]

In summary, when a biliocolonic fistula is suspected at ERCP, a colonoscopy may easily lead to the correct preoperative diagnosis.

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MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the September issue of the Netherlands Journal of Medicine 2008 (available online on PubMed since 22 September 2008).

Article	Hits
EDITORIAL	
Copper: two sides of the same coin	60
REVIEWS	
Strategies for primary and secondary stroke prevention in atrial fibrillation	123
Vascular liver disorders (I): diagnosis, treatment and prognosis of Budd-Chiari syndrome	92
ORIGINAL ARTICLE	
Defective interferon-gamma production in patients with hairy cell leukaemia	41
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MONTHLY NJM ONLINE HITLIST	
For all articles published in May 2008	41
Total	**937**

Netherlands
The Journal of Medicine

PHOTO QUIZ

An adult with lower abdominal pain

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CASE REPORT

A 39-year-old male presented to our emergency department with a history of lower abdominal pain, vomiting and no stools for five days. Physical examination showed a not acutely ill patient with a normal blood pressure of 130/80 mmHg, a pulse of 75 beats/min and a body temperature of 37.2°C. Abdominal examination revealed sparse high-pitched bowel sounds, hypertympanic percussion and a distended abdomen. The pain was diffusely located in the lower abdomen. Laboratory investigations showed a normal blood count (haemoglobin 7.7 mmol/l, mean cell volume 71 fl), slightly abnormal renal function (urea 10.6 mmol/l, creatinine 99 µmol/l), normal leucocytes, no elevated liver enzymes and normal C-reactive protein level. A plain abdominal radiograph showed the presence of an ileus with dilated small bowel loops. A contrast-enhanced abdominal CT scan revealed abnormalities in the terminal ileum (*figure 1A* and *1B*).

Figure 1A. *CT scan (axial view): lower abdomen*

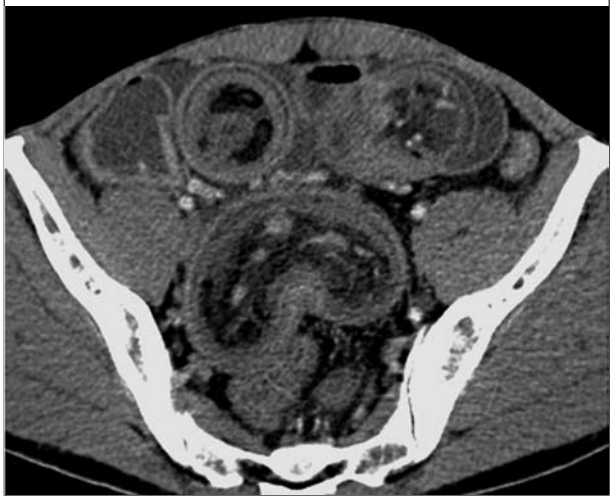
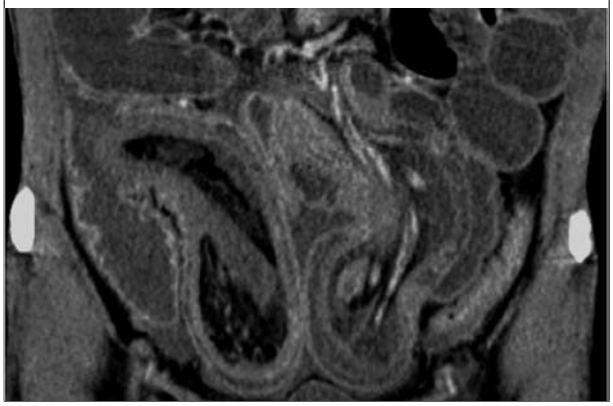


Figure 1B. *CT scan (coronal view): lower abdomen*



WHAT IS YOUR DIAGNOSIS?

See page 496 for the answer to this photo quiz.

DIAGNOSIS

On contrast-enhanced abdominal CT scan, the ileum appears as a target-like or sausage-shaped mass (*figure 1A*). There is a bowel-within-bowel configuration with mesenteric fat and (contrast-enhanced) mesenteric vessels within the terminal ileum (*figure 1B*). These findings are pathognomonic for an intussusception. On emergency laparotomy, an ileo-ileal intussusception was found and resected. Pathological examination of the resected bowel confirmed the diagnosis of intussusception (*figure 2*). No intraluminal lesion acting as a lead point for the intussusception was seen. The patient had an uneventful recovery.

Intussusception is a rare occurrence in adults and is defined as an invagination of a proximal segment of bowel (intussusceptum) into lumen of a distal segment (intussuscipiens). Approximately 5% of all intussusceptions occur in adults, accounting for 1% of all bowel obstructions.[1] It has often been stated that intestinal intussusception in adults is frequently caused by underlying disease with 70 to 90% of cases having a demonstrable cause based on discharge diagnosis or surgical results.[1,2]

Figure 2. *Resected distal ileum revealed necrosis (brownish discoloration) of the distal intussusceptum*

Intraluminal lesions alter normal bowel peristalsis and form leading edges for the intussusceptum.[3] The most common cause of benign enteric intussusception is postoperative adhesions, but Meckel's diverticulum, lipoma, polyps (associated with Peutz-Jeghers syndrome) and neurofibroma are also described as benign leading points. Malignant enteric lesions consisted primarily of metastatic disease. Metastatic melanoma, metastatic lymphoma and metastatic sarcoma are described as cause of enteric intussusceptions.

Although intussusceptions present acutely in children, adults may also present with acute, intermittent, or chronic problems. The predominant symptoms are usually those of bowel obstruction with nausea, vomiting and abdominal pain. Consequently, intussusception is often misdiagnosed initially in the adult population. The disease can be complicated by obstruction and haemorrhage leading to infarction and necrosis of the intussusceptum, which in severe cases may lead to perforation and peritonitis.

The widespread application of ultrasound and computed tomography in different clinical situations has increased the preoperative detection of intussusception. The CT scan is the most accurate technique, showing intussusception in approximately 80% of the cases.[1]

No treatment is needed for transient, nonobstructing enteric intussusception. In obstructed enteric intussusception resection is the only treatment option.

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The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the editor are welcomed.

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