

TOPICAL REVIEW

Prostacyclins in pulmonary hypertension treatment

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Abstract

Pulmonary hypertension is a rare, treacherous disease affecting the lungs and heart. Elevated pulmonary artery pressure (above 2.67 kPa) and pathologically high pulmonary vascular resistance are characteristic for this disease. This disease is insidiously progressive and often leads to sudden death mainly in middle and younger middle ages.

Exhausting the traditional conservative means of treatment, lung/heart-lung transplantation offers the only possibility to improve the quality of patient's life.

Nowadays more and more reports about the successful application of intravenous prostacyclin for treatment of this disease appear in specialized literature. Epoprostenol (prostacyclin PGI₂) represents a new, potent drug for the treatment of pulmonary hypertension.

The objective of this paper is to introduce prostacyclin PGI₂ to experts and demonstrate new possibilities, procedures, trends in treatment of pulmonary hypertension. (Tab. 1, Ref. 30.)

Key words: primary pulmonary hypertension, secondary pulmonary hypertension, poprostenol (prostacyclin PGI₂), lung transplantation, heart-lung transplantation.

Abbreviations: PPH – primary pulmonary hypertension, SPH – secondary pulmonary hypertension, PVR – pulmonary vascular resistance, PAP – pulmonary artery pressure, mPAP – mean pulmonary artery pressure, CO – cardiac output, CI – cardiac index, TK – systemic arterial pressure, PG – prostaglandins, TX – thromboxane, ARDS – adult respiratory distress syndrome, NO – nitric oxide, paO₂ – partial arterial oxygen pressure, paCO₂ – partial arterial carbon dioxide pressure, KATP – potassium-adenosine triphosphate channel, KCa – potassium-calcium channel, TEA – chronic thromboembolic disease, NIH – National Institute of Health

Pulmonary hypertension is a rare disease affecting the lungs and heart. Pulmonary vessel narrowing causes pressure increase in the pulmonary artery. This increase results in imbalances in pulmonary circulation, reduction in gas exchange and overload of the right ventricle, which leads to its failure (Dieška et al, 1990; Rubin, 1997).

The patients who suffer this disease are dyspneic and have a reduced tolerance of physical activity. This disease was progressive tendency leading up to the sudden premature death. Conservative as well as surgical treatment in Slovakia is complicated, expensive and not accessible for everyone. A lot of drugs and treatment modalities are still undergoing clinical testing and are

the subject of testing and discussion. For many patients and their attending physicians the only remaining possibility is lung or heart-lung transplantation (Rubin, 1997; Pereszlenyi et al, 2002).

Very often the first symptoms, such as: sudden occurrence of dyspnea and quick exhaustion after a minimum activity — are interpreted by the affected patients (and their physicians) as „non-specific“ signs of other diseases, and that is why the exact diagnosis is often made later and the correct treatment is late. It is not rare that a patient with this disease is considered to be non-trained (Dieška et al, 1990; Rubin, 1997).

The exact etiology, reasons of origin of this disease are still not known in details. This disease can be inherited and can occur in several generations of the family. This is why it is recommended to examine the family members of the patient (Dieška et al, 1990; Rubin, 1997).

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The objective of this paper is to highlight some difficulties connected with early diagnosis, to introduce new possibilities in treatment of this rare and treacherous disease.

Definition, etiology

The term Pulmonary Hypertension indicates an increase of the mean pulmonary artery pressure above 2.67 kPa (20 mmHg) in the supin position at rest (Dieška et al, 1990; Rubin, 1997; Pereszlényi et al, 2002; Widimský, 1976). According to Widimský pulmonary hypertension can be divided into three basic types:

1. Hyperkinetic type of pulmonary hypertension,
 2. Passive, post-capillary type of pulmonary hypertension,
 3. Pre-capillary type of pulmonary hypertension:
- a) restriction form caused by restriction of pulmonary capillary bed;
 - b) active form, mainly developed by vasoconstriction of pulmonary capillary bed;
 - c) obstructive form, developed by mechanical obstruction in pulmonary artery branches.

Primary pulmonary hypertension (PPH) as a nosologic unit is an obstruction form of pre-capillary pulmonary hypertension. This disease (as it was already mentioned in the introduction) is characterized by pathologically increased pulmonary vascular resistance and elevated pulmonary artery pressure, which can not be explained by post mortem by lung or heart disease, or systemic disease, which could cause pathological changes in pulmonary vessels (Dieška et al, 1990; Widimský, 1976; Widimský et al, 1987; Kordač et al, 1991).

With any cause of pulmonary hypertension, if it is not stabilized, it is probable that the pulmonary vessels' walls will change secondarily, and the smooth muscle progresses due to the increased tension and work of vessel walls. The intima reacts to the increased pressure by proliferation (similarly as arterioles in a greater circulation at a systemic hypertension). With these anatomic changes pressure in pulmonary artery further increases, so that severe pulmonary hypertension develops.

The basic hemodynamic sign of pulmonary hypertension is an increased vascular resistance without any reason. The pulmonary vascular resistance is almost 18 times higher than normal. Systolic pressure in the pulmonary artery is often more than 13 kPa (100 mmHg). With exercise the pressures increases, further while pulmonary vascular resistance does not change. Cardiac index is often reduced and pressure in left atrium is normal. As a consequence of the reduced cardiac index, systemic pressure is generally more likely to be reduced. The end-diastolic pressure in the right ventricle is elevated. Blood oxygen saturation is moderately reduced and $p\text{CO}_2$ is also reduced as a consequence of hyperventilation (Dieška et al, 1990; Widimský, 1976; Widimský et al, 1987).

Treatment

The classical treatment described in the Internal Medicine textbook consists of infusion of acetylcholine, tolasoline, and isoproterenol. With long-term peroral hydralazine the pulmonary

vascular resistance was expected to decrease. Favorable results after sublingual application of isoproterenol and peroral supply of phentolamine were also expected. In several cases cardiac output was increased by vasodilatation, but pulmonary artery pressure did not decrease. Success was not obtained with anticoagulation treatment (Dieška et al, 1990; Rubin, 1997; Kordač et al, 1991).

Prostacyclin and lung transplantation

Recently more and more reports about successful treatment of pulmonary hypertension (primary, secondary) by intravenous prostacyclin – epoprostenol application can be found in the literature (Rubin, 1997; Galie et al, 2001). As already mentioned in the introduction, only lung or heart-lung transplantation seemed to be the solution for the affected patients (Rubin, 1997; Pereszlényi et al, 2002, 2002, 2001).

After introduction of prostacyclin in the treatment of pulmonary hypertension and numerous promising reports about the successful treatment by this drug, the indication and timing of lung transplantation have changed. According to the latest guidelines (Pereszlényi et al, 2000; Arcasoy and Kotloff, 1999; Trulock, 1993), lung transplantation is indicated for patients with pulmonary hypertension after the failure of intensive medical therapy – especially after the failure of intravenous epoprostenol (Tab. 1).

Whether this treatment has a long-term therapeutic effect, or it serves as the so-called bridging during the demanding pre-transplantation period, it is generally accepted, that this treatment (or prostacyclin test) must be tried. It is a pre-condition before putting patients on the waiting list, that prostacyclin treatment must be tried.

Now, a brief overview about the use and application of prostacyclin will be presented.

Brief overview of prostacyclin in literature

In 1987 Jones DK et al published a paper – a group of 10 PPH patients, and he compares the results after the application of intravenous prostacyclin (epoprostenol, PGI_2) with the results, where peroral vasodilators and anticoagulants (conventional treatment) were used. All these patients had indication for heart-lung transplantation. The authors proved that the short term administration of intravenous epoprostenol (mean dose 5.5 ng/kg/min) increased the mean cardiac index (CI), improved pulmonary artery oxygen saturation from 48 % to 57 %, and increased calculated tissue oxygen delivery from 10 to 11.8 ml/kg/min. The mean pulmonary artery pressure (mPAP) and the mean system pressure decreased. Continued intravenous infusion of epoprostenol for 1–25 months was associated with subjective and clinical improvement. Two patients died on treatment, three have undergone heart-lung transplantation, and in five the treatment continued during the time when the article was published (Jones et al, 1987).

In 1989 in the “Chest” journal the same author (Jones DK) report about a group of 23 patients with similar results as in his previous paper. It must be mentioned that in this case it was not a homogeneous PPH group, there were also second-

Tab. 1. Guidelines for Timing referral.

COPD (+alfa 1 - antitrypsin deficiency emphysema)
FEV 1 < 25 % predicted
Clinically significant hypoxemia
Hypercapnia
Secondary pulmonary hypertension
Clinical course: rapid rate of decline of FEV 1 or life-threatening exacerbations
Cystic fibrosis
FEV 1 < 30 % predicted
or FEV 1 > 30 % with rapidly declining lung function
Hypercapnia
Clinical course: increasing frequency and severity of exacerbations, progressive weight loss
Idiopathic pulmonary fibrosis
VC, TLC < 60-65 % predicted
Symptomatic disease unresponsive to medical therapy
Secondary pulmonary hypertension
Clinical, radiographic, or physiologic progression on medical therapy
Primary pulmonary hypertension
NYHA functional class III or IV
Mean right atrial pressure > 10 mmHg
Mean pulmonary arterial pressure > 50 mmHg
Cardiac index < 2.5 L/min/m ²
Failure of intensive medical therapy (especially intravenous epoprostenol)

ary pulmonary hypertension (SPH) patients included (Jones et al, 1989).

Pascual JMS et al reported about a successful prostacyclin pulmonary hypertension therapy developed after heart transplantation. In 9 patients (from 50), who underwent heart transplantation, dramatic right ventricular failure developed. Prostacyclin was started, and the dose increased from 0.5 to 5.0 ng/kg/min, which led to the desired hemodynamic effect (increase of CI, reduction of mPAP). The use of prostacyclin enabled the weaning of other drugs within a 48-hour period with no side effects and no worsening of the hemodynamic conditions after discontinuation of prostacyclin. All the patients with right ventricular failure treated were successfully managed (Pascual et al, 1990).

Rubin LJ et al (1990) reported about the results of a prospective, randomized trial, where 24 PPH patients underwent continuous intravenous prostacyclin treatment. 19 patients successfully completed the study, 4 patients died during the study and 1 was excluded from the study due to a severe side effect – pulmonary edema. The most significant contribution of this study was that continuous intravenous prostacyclin was administered for the first time by portable infusion pump during a period of 18 months (Rubin et al, 1990).

Lewis J. Rubin (1992) from the University of Maryland, Baltimore, in the journal “Drugs” introduced prostacyclin in details as a potent pulmonary vasodilating agent, pointed out the possibility of its application even during the period of several

years, and for the first time talked about prostacyclin treatment as “bridging” to lung transplantation.

In 1992 Schranz et al published a prospective cohort study, where 14 infants (2 to 12 months old) after cardiac surgery were successfully treated by tolazoline or prostacyclin. According to the protocol tolazoline was administered as a bolus of 0.5 mg/kg for treatment of persistent pulmonary hypertension or acute pulmonary hypertensive crisis. If its effectiveness was proved after 30 mins by hemodynamic measurements, continuous iv infusion of 0.5 mg/kg/hr was established. If tolazoline treatment did not fulfill the criteria for pulmonary vasodilatation, prostacyclin was given by continuous iv infusion at a starting rate of 5 ng/kg/min, followed by 10–15 ng/kg/min. From the total 14 patients, 13 were successfully treated. The authors also described that transient withdrawal of prostacyclin in 5 infants led to significant worsening of hemodynamic parameters (Schranz et al, 1992).

The objective of another prospective study published in 1993 was to determine whether epoprostenol (prostacyclin, PGI₂) or heart-lung transplantation (HLT), or both improves survival of patients with severe pulmonary hypertension. Forty-four patients were studied; 25 among them received continuous epoprostenol over a four year period. The patients were tested every three month by a 12-minute walking test. The patients, who did not receive prostacyclin, were treated with anticoagulants and nifedipine (<20 mg) or diltiazem (>120 mg) three times a day. The patients of both groups were further prepared for the transplantation. When physical disability occurred, the patient (of prostacyclin group) was urgently listed for transplantation. The results of successful therapeutic intervention (epoprostenol, HLT), led to improve survival, and were compared with the results of survival in Mayo clinic (120 patients). One-year survival was better in the prostacyclin group, however after two years the survival in both groups was identical. Most of the benefit was conferred by epoprostenol, which prolonged survival twofold from median time of 8 to 17 months and thus doubled the chances of obtaining an organ for transplantation (Higenbottam et al, 1993).

Walmrath et al (1993) published a paper about the positive effect of prostacyclin in ARDS treatment (Adult Respiratory Distress Syndrome). The importance of this study is in the proof of the selective effect of aerosolized prostacyclin on pulmonary perfusion and ventilation. Prostacyclin given this way lowered the mean pulmonary artery pressure (mPAP), pulmonary vascular resistance by 30 %, and systemic arterial pressure slightly from 76.8 to 74.5 mmHg (Walmrath et al, 1993).

Olschewski et al (1996) continued studying the effects of aerosolized prostacyclin. The objective of his study was to compare the effects of aerosolization of prostacyclin and its stable analogue iloprost with nasal oxygen, inhaled nitric oxide (NO) and intravenous prostacyclin on the hemodynamics and gas exchange in patients with severe pulmonary hypertension. Results: aerosolized prostacyclin decreased pulmonary artery pressure in 6 patients from (mean±SE) 62.3±4.1 mmHg to 50.8±5.5 mmHg and reduced pulmonary vascular resistance from 1721±253 dyne/s cm⁻⁵ to 1019±203 dyne/s cm⁻⁵, and increased cardiac output from 2.75±0.21 L/min to 4.11±0.54 L/min, mixed venous

oxygen saturation from $51.1 \pm 3.4\%$ to $66.3 \pm 4.1\%$ and arterial oxygen saturation from $90.6 \pm 2.7\%$ to $93.8 \pm 2.3\%$ ($p < 0.05$ for all changes). Mean systemic arterial pressure was only slightly affected. The responses lasted from 10 to 13 minutes after inhalation was terminated. Aerosolized iloprost had an identical efficacy profile but was associated with a longer duration of the pulmonary vasodilatory effect (60 min to 120 min). In comparison, intravenous prostacyclin reduced pulmonary vascular resistance, slightly reduced systemic artery pressure, however no clinically significant decrease in pulmonary artery pressure was recorded. Nitric oxide and oxygen were less potent pulmonary dilators in these patients. In one patient, one year of therapy with aerosolized iloprost (100 $\mu\text{g}/\text{d}$ in six aerosol doses) resulted in sustained efficacy of the inhaled vasodilator regimen and clinical improvement (Olschewski et al, 1996).

In this connection it is necessary to point out further work of Warren and Higenbottam published in 1996. This was actually a letter to editor with a specific regard to caution when nitric oxide is applied. The authors warned about the lack of standard guidelines when using this gas, the lack of storage information. They also pointed out that the products of gas fragmentation contain toxic and potential carcinogenic elements. This article also deals with the known “rebound phenomenon” with a severe stage of pulmonary hypertension after gas dose reduction (Warren and Higenbottam, 1996).

The increased resistance in pulmonary vascular bed as a consequence of endothelial damage is a reason of pulmonary hypertension at patients with systemic sclerosis. Rolla et al assumed that the reason of this damage is NO production and releasing failure (NO is being produced by different cells of respiratory system, mainly by pulmonary vessels endothelium). In patients affected by systemic sclerosis and pulmonary hypertension, lower concentration of NO in expired air was found. Measuring of NO concentration in the expired air after pharmacologic stimulation offers a new non-invasive functional test of the endothelium. According to this, then, it could be possible to enable identification of such patients who could profit from vasodilator treatment. In two patients with systemic sclerosis and pulmonary hypertension the authors tested this hypothesis. The NO concentration in the expired air in both cases was 2.8 and 3.4 ppb, respectively. Later both patients were given L-Arginine (precursor of NO) and on the second day Glycerin nitrate was given for 20 minutes. In one patient 30 minutes later the NO concentration in the expired air was 6.3 and 8.2 ppb, respectively. After infusion of physiologic solution no such effect was registered. In the second patient no change in the NO concentration in the expired air was discovered. In the next part of the test an aerosolized iloprost (20 μg) was compared to the physiologic solution (given as aerosol). 30 minutes after iloprost inhalation the authors recorded a significant increase of NO concentration in the expired air in the first patient (from 2.2 to 9.5 ppb). Arterial partial pressure O_2 (paO_2) increased from the original 65 to 80 mmHg and pulmonary artery pressure decreased from 54 to 29 mmHg. No changes in heart frequency and arterial systemic pressure were recorded. No significant changes were recorded

in the second patient (where physiological solution was given as control). An increase of NO concentration in expired air after pharmacological stimulation is a clear proof of the smooth muscle of pulmonary vessels' response to vasodilator iloprost stimulation. The non-increase of NO concentration here is generally being explained with the missing vasodilative reaction to inhaled iloprost. It is not probable that pulmonary vessels' vasodilatation (in first patient) depends ONLY on the increased expired NO concentration, because a similar NO concentration increase had been already recorded also after L-Arginine or Glyceril-Trinitrate infusions, despite the fact that after their application no influence on pulmonary artery pressure was observed. The relaxation effect of iloprost (as proved in the experiment on isolated perfusion of a rat's lung) is realized through KATP and KCa channels and only seldom also by NO release. On the basis of the positive results of the above-mentioned test the first patient was treated with aerosolized iloprost (100 $\mu\text{g}/\text{d}$ in five doses). Three months later a significant improvement of hemodynamic parameters in pulmonary circulation was observed. Following the results authors recommended to apply a pharmacological stimulation test for potential respondent identification (Rolla et al, 1998).

Higenbottam et al in 1998 compared the effect of prostacyclin (epoprostenol PGI_2) with its analogue – iloprost in the treatment of severe pulmonary hypertension in eight patients (5 patients with PPH and 3 patients with chronic thromboembolic pulmonary hypertension (TEA)). All patients underwent right heart catheterisation. The results of this exam were: mean (SEM) right atrial pressure was 9.9 (2.2) mmHg, mPAP=67.4 (3.0) mmHg, CI=1.75 (0.13) l/min/m² and mixed venous oxygen saturation was 59.1 (3.1) %. Continuous intravenous epoprostenol or iloprost was given for phase I (three to six weeks); the patients then were crossed over to receive the alternative drug in an equivalent phase II. Exercise tolerance was measured at baseline and at the end of phase I and II with a 12-minute walk. Distance covered, rest period, percentage drop in arterial oxygen saturation (ΔSaO_2 %) and percentage rise in heart rate ($\Delta \text{HR}\%$) were also measured. Results: The walking distance covered rose from {mean (SEM)} 407.5 (73) to 591 (46) m with PGI_2 and to 602.5 (60) m while on iloprost. Rest period decreased from 192 (73) seconds at baseline to 16 (16) seconds with PGI_2 and to 58 (34) seconds with iloprost. $\Delta \text{HR}\%$ was 37.5 (6) % at baseline, 35 (3) % on PGI_2 , and 24 (6) % on iloprost. It must be concluded that the results were highly significant (Higenbottam et al, 1998).

In 1998 Olschewski et al reported on a 45-year old female patient with PPH, pneumonia, decompensated right heart failure (ascites, pleural effusion), circulatory shock and commencing renal and hepatic failure, despite maximum therapy including the use of catecholamines. Iloprost (150 $\mu\text{g}/\text{d}$) and NO were added to the therapy. After this treatment the following parameters improved: mPAP decreased from 65 to 61 mmHg, CI increased from 1.25 to 1.85 l/min/m², PVR decreased from 2416 to 1549 dyn/s/cm⁵. Both methods increased the arterial pO_2 but did not change the systemic arterial pressure. During repeated inhala-

tions with iloprost, the baseline hemodynamics and gas exchange improved dramatically, renal and liver functions normalized. During one year of continued therapy, the clinical status improved, concomitant with improved hemodynamics, and the patient was taken off the transplantation list (Olschewski et al, 1998).

Among the experimental papers, the study of Kleen from Munich University, Germany (1998) is of specific interest. The authors compared the effect of inhaled prostacyclin PGI₂ with the effect of prostaglandin PGE₁ in aerosolized and intravenous forms. The aerosolized form of PGI₂ had a significant effect to decrease mPAP and pulmonary vascular resistance. Such an effect after PGE₁ application was not observed after aerosol nor after intravenous administration (Kleen et al, 1998).

Pulmonary hypertension is a serious life-threatening disease. According to the National Institute of Health (NIH) registry the average survival is 2.5 years (Rubin, 1997; D'Alonzo et al, 1991).

According to the other statistics of this Institute, the 5-year survival rate among patients (in New York Heart Association classes III and IV), treated with epoprostenol (54 %), was twice that of matched historical control patients (27 %) (Rubin et al, 1990).

In the future long-term therapy with stable prostacyclin analogues (in inhaled, transdermal, or oral form) or with inhaled nitric oxide appears to be promising. In order to identify molecular mechanisms responsible for pulmonary hypertension, research of the genetic mechanisms may be very helpful (Rubin, 1997; Saji et al, 1996; Snell et al, 1995).

Lung or heart-lung transplantation, respectively, has an irreplaceable position after the failure of conservative treatment of pulmonary hypertension (Pereszlenyi et al, 2000, 2001). The development in this area includes less invasive operating techniques and newer treatment procedures – e.g. extracorporeal membrane oxygenation during the lung transplantation procedure (Pereszlenyi et al, 2000, 2001, 2002). Future studies will show the value of this approach and help perfect new treatments.

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NEW BOOKS

Kuntz E, Kuntz HD. *Hepatology, Principles and Practice*. Berlin—Heidelberg—New York, Springer Verlag 2002, 380 coloured Figures, 276 Tables, 40 Chapters, 825 pages.

The book *Hepatology, Principles and Practice*, a common work of the father and son Erwin & Hans-Dieter Kuntz, is a fresh and encouraging contribution to the already remarkable list of comprehensive monographs devoted to hepatology. It underlines an appropriate interest the renowned international publisher — Springer Verlag devotes to this rapidly growing and prospective field of medicine, hopefully maturing towards the full recognition as a distinctive medical specialty in Europe and world-wide. This could be rightly expected to happen in not a too distant future. The book itself both nicely illustrates and supports these progressive considerations.

The authors with a strong professional background in hepatology and possessing an outstanding didactical mastership, have created a readable, comprehensive work about contemporary hepatology, which has substantially profited also from their, already extensive, editorial experience (documented also by a recent German edition of the book, published in the year 1998 by Johann Ambrosius Barber Vlg., Heidelberg).

The main author and editor of the book — Prof. E. Kuntz has proven himself being not only an outstanding and enthusiastic worker in the field of the study of the liver and its diseases and therapies, but — to my personal knowledge — he also has acted many times as a great humanist and internationalist. I am proud of having been given the possibility to be a colleague and friend of this distinguished, but modest personality, who has devoted much of his time and effort also to the activities in the Central and East European region. His participation in the 1st International Symposium on Hepato-Pharmacology „Liver & Drugs '94“ in Bratislava, as well as his personal support to development of hepatology in Slovakia, have contributed to the fact, that Slovakia, among the first countries in Europe and beyond, has acknowledged the need of, and implemented in practice the professional profilation and postgraduate education and training of a distinctive medical specialist in hepatology — the hepatologist.

A moving detail in the introductory part of the book is Prof. E. Kuntz's dedication of the 1st German edition to his beloved son and co-author of the book, who has passed away just shortly before its first publication, as well as his tribute and dedication of the present edition to the great supporter and “classical personality” of contemporary European and world hepatology — Dr. Herbert Falk. We share also this personal appreciation of the author.

The book itself contains of 40 distinctive chapters that cover successfully the broad and quickly growing field of modern hepatology, starting from both important and interesting historical remarks and concluding with a comprehensive chapter on therapy of liver diseases. The well-balanced and complex overview of the topics covered; the plentitude of clearly arranged figures and schemes, most of them being set up in colour, supporting convincingly didactic aims of the authors; an impressive number of a good quality colour histopathological and clinical photodocumentation; and an extensive list of references to both substantial „classic“ and recent papers; these are the most important features of the book that are very helpful to a quick and reliable orientation of the reader in both the development and “status quo” of contemporary clinical hepatology. The bibliography of the book contains about 7.300 references cited in the text.

I have especially liked thoughtfully elaborated schemes of the diagnostic and therapeutic algorithms that are contributing as an indispensable part to the high didactic quality of the publication. The „lovers“ of the “evidence-based” approach will find in the book enough material for their study and referencing, but authors do not avoid the chance of taking a „risk“ of expressing their own personal views on various topics under discussion. This personal approach adds a special value to the book, especially in comparison to other textbooks or monographs of similar format enlisting dozens of contributors working under meticulous leadership of distinguished editorial boards.

I would like to underline the informative, didactical and „practical“ value of the book, its easy-to-review arrangement and intelligibility that allow its use in a broad setting of both undergraduate and postgraduate education and training of physicians — medical students, general practitioners, internists, gastroenterologists and hepatologists.

In conclusion, I would like to refer to an evaluation of Prof. Ch.S. Lieber (Mount Sinai School of Medicine, New York) given in the foreword: “This volume brilliantly achieves the basic aim of its authors, which is to guide user from “seeing” to “understanding” and finally to “acting”. (...) [it] will undoubtedly become an international landmark.” The book, because of its clarity, comprehensiveness, orientation to clinical practice, and relatively friendly pricing, is to be recommended to everyone in need of a practical and comprehensive manual of hepatology for his/her education and training, as well as for his/her everyday's practice of hepatology.

J. Holomáň