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Transesophageal Echocardiographic Assessment of Right Heart Hemodynamics During High-Frequency Jet Ventilation

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Study Objective: *To evaluate right ventricular dimensions and function by echocardiography in anesthetized patients during superimposed high-frequency jet ventilation (HFJV).*
Design: *Prospective clinical study.*
Setting: *University hospital operating room.*
Patients: *20 ASA physical status I patients undergoing elective minor otorhinolaryngological surgery, and undergoing conventional mechanical ventilation with subsequent superimposed HFJV.*
Interventions: *Two-dimensional transesophageal echocardiography with a 5-MHz multiplane transducer to determine right ventricular dimensions and function from a mid-esophageal view. Insertion of a radial artery catheter for monitoring blood pressure and blood gases.*
Measurements and Main Results: *Heart rate, mean arterial blood pressure, and right ventricular end-diastolic and end-systolic volumes determined by echocardiography, stroke volume, and ejection fraction. Measurements were performed after 10 minutes of conventional positive pressure ventilation (control) and after 10 minutes of subsequent superimposed HFJV at similar peak and positive end-expiratory airway pressures. Right ventricular systolic and diastolic volumes, stroke volume, and ejection fraction did not reveal statistical significant differences after transition to HFJV. Interventricular septum did not show any abnormalities in motion. In contrast, interatrial septum demonstrated momentary mid-systolic bows toward the left atrium in 9 of 17 patients (53%) during conventional ventilation, but in 15 of 17 patients (88%) during jet ventilation. Heart rate and mean arterial blood pressure remained unchanged, but arterial oxygen tension values were higher and arterical carbon dioxide tension values lower during HFJV.*
Conclusion: *Transesophageal echocardiographic evaluation of right heart hemodynamics did not show any significant difference after transition of ventilation to superimposed HFJV applying similar airway pressures. Furthermore, superimposed HFJV was safe and effective, it improved oxygenation, and it faciliated carbon dioxide elimination.* © 1999 by Elsevier Science Inc.

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Introduction

Since its original description by Klain *et al.*,[1] high-frequency jet ventilation (HFJV) has been proposed as an alternative ventilatory technique during laryngeal and pulmonary surgery, as ventilatory support in patients with bronchopleural fistulae, and for treatment of pulmonary insufficiency.[2–5] Although regular monofrequent HFJV enables gas exchange in patients with normal lung function during endolaryngeal surgery,[6] the combination of HFJV and conventional ventilation has been favored in the presence of compromized pulmonary function.[7] High-frequency jet ventilation is defined by the pulsed application of small tidal volumes (V_Ts) (2 to 5 ml/kg) at a high rate (1 to 20 Hz) via small-bore cannulae from a high-pressure source. High-frequency jet ventilation has been successfully applied in anesthesia and in intensive care units because the smaller V_Ts required to maintain oxygenation may reduce cardiocirculatory depression. However, data concerning cardiac output (CO) during jet ventilation are conflicting. Chiaranda *et al.*[8] found an augmentation of left ventricular (LV) CO, whereas Traverse *et al.*[9] reported a decrease in CO. Recent studies in patients undergoing lung transplantation for severe, end-stage obstructive lung disease revealed no significant difference between conventional ventilation and HFJV with respect to stroke volume (SV), CO, and blood pressure (BP).[10] We anticipated that, with transesophageal echocardiography (TEE), the proximity of the probe to the cardiac structures and the use of a high-frequency (HF) transducer would clearly visualize the heart for assessment of the impact of ventilation on right heart hemodynamics. The goal of the present study was to investigate right ventricular (RV) volumes and function after transition of ventilation to superimposed HFJV (SHFJV), which represents a new technique of combined HFJV.

Materials and Methods

After approval by the ethics committee of the Medical faculty of the University of Vienna and obtaining written informed consent, 20 heart and lung healthy patients (9 men and 11 women; ASA physical status I; age 30 ± 8 years, body weight 71.8 ± 12.7 kg) without esophageal or gastric disease undergoing minor otorhinolaryngological surgery were admitted into the study. A radial artery catheter was inserted for blood gas analysis and BP monitoring. After induction of total intravenous anesthesia (propofol/fentanyl, vecuronium) patients tracheas were intubated with a conventional tracheal tube (ID 8.0 cm). Continuous positive pressure ventilation (PPV) was applied with a V_T of 10 ml/kg, respiratory rate = 10 cycles/min, inspiratory to expiratory time ratio = 1/1.5, positive end-expiratory pressure (PEEP) of 5 cm H_2O, and an inspired oxygen fraction (FIO_2) of 0.3, using a standard respirator (Cicero, Dräger, Luebeck, Germany). During ventilation, anesthesia was maintained with a continuous propofol infusion (8 mg/kg/hr) and a second dose of vecuronium (2 mg). After 10 minutes of continuous PPV, SHFJV, which is a new mode of combined HFJV, was initiated.[4] Superimposed high-frequency jet ventilation is characterized by the simultaneous application of a low-frequency (LF) and an HF jet stream delivered via two separate cannulae of a special jet adapter connected to the standard endotracheal tube (*Figure 1*). The continuous HF jet pulses (10 Hz) were applied during the inspiratory and expiratory phase of LF jet ventilation (10/min). Low-frequency jet ventilation resulted in phasic airway pressure changes and thoracic excursions analogous to conventional ventilation. The jet adapter (T-connector, Ruesch AG, Kernen, Germany), specially designed to deliver SHFJV, consisted of a T-piece and four central small-bore (ID 1 mm) cannulae measuring 7, 7.5, 8.5, and 18.5 cm in length, for application of the LF jet stream, HF jet pulses, gas humidification, and airway pressure monitoring, respectively.[11] For gas entrainment around the jet nozzles due to the Venturi effect, a bias flow (15 L/min) was led through the cross part of the T-piece open to the atmosphere. Noncompliant Teflon tubing connected the ventilator outputs to the cannulae. An electronic prototype jet ventilator (Alex 1, Festo C. Reiner, Austria) connected to the central gas supply provided two pulsed jet streams gated by solenoid valves and one bias flow. The duty cycle and opening frequency of these valves, one acting as a HF flow interrupter, were controlled by an electronic timer. The inspiratory to expiratory time ratio of the LF jet stream was set to 1:1.5, and the inspiratory time of the HF jet pulses was 50%. The FIO_2 of all gas flows was set to 0.3. The ventilator had integrated manometers for measurement of adjustable driving pressures and airway pressures. It allowed adjustment of driving pressures of both jet streams (0 to 3.5 bar), resulting in total flow rates of up to 50 L/min. Gradual increase of driving pressures of the HF and LF jet streams served to increase applied V_T and airway pressures to the desired levels of peak inspiratory pressure (PIP) and PEEP, respectively. The V_T provided by the jet ventilator was augmented by the amount of gas entrained around the cannulae from the continuous bias flow. Generation of PEEP by the HF jet stream did not include the use of a PEEP valve. The expiration phase was free to the bias flow. An alarm system was integrated into the ventilator to limit peak airway pressure. The airway pressure monitoring cannula of the jet adapter enabled measurement of airway pressures 10 cm downstream from the jet nozzles, inside the endotracheal tube. Thus, SHFJV represented a pressure-controlled, pressure-limited, and time-cycled open-ventilation technique. Humidification and warming of inspiratory gases were achieved with a standard hot-water humidifier (Aquapor, type 8406640, Draeger, Luebeck, Germany) integrated into the bias flow. Second, heated 0.9% saline (20 ml/hr) was administered continuously via the appropriate cannula with its side outlet at the distal end positioned toward the HF injector for humidification of gas by nebulization and propulsion by the HF jet stream.

Echocardiographic investigations were carried out by

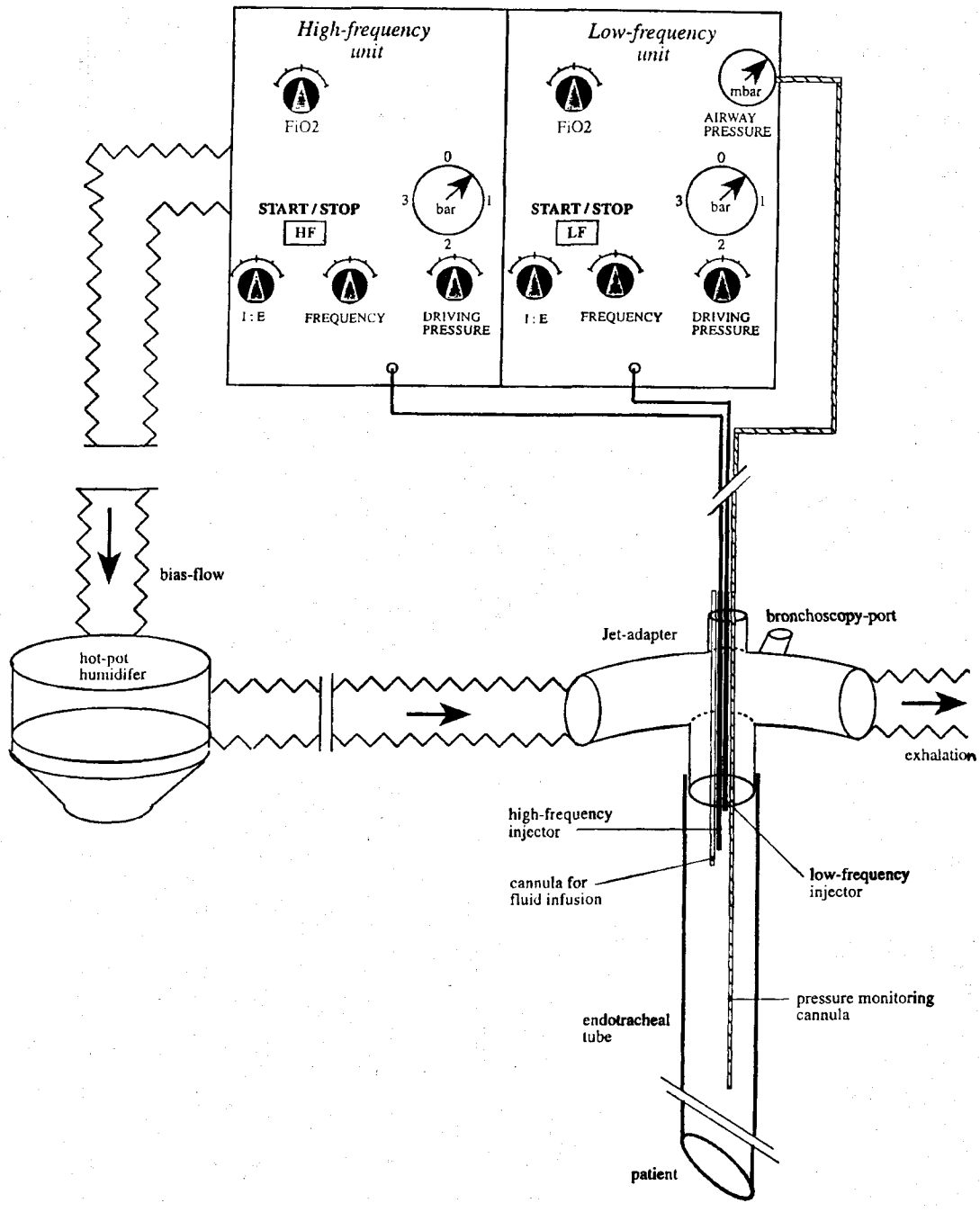

Figure 1. Schematic illustration of combined superimposed high-frequency jet ventilation using a high-frequency (HF) and a low-frequency (LF) jet stream and a special jet adapter for connection with the standard endotracheal tube. The jet ventilator consists of an HF and an LF unit, and it provides an additional continuous bias flow for gas entrainment. The jet adapter consists of a T-piece with four central cannulae of different lengths for application of two jet streams, gas humidification, and airway pressure monitoring inside the tracheal tube. The warmed and humidified bias flow is led through the cross part of the T-piece and is open to the atmosphere. For warming and humidification of inspiratory gases a standard humidifier and a separate cannula for fluid nebulization are integrated. FiO_2 = inspired oxygen concentration.

two expert observers, one cardiologist and one anesthesiologist, using a Hewlett-Packard ultrasound system (HP Sonos 1500, Hewlett-Packard, Vienna, Austria) and its integrated software, employing a 5-MHz transesophageal multiplane probe (Hewlett-Packard, Andover, MA). After anesthesia induction, the multiplane probe was inserted into the esophagus. After routine examination of the chambers and valves of the heart, TEE images of the RV were obtained from a mid-esophageal view. After 10 minutes of adaptation to each ventilatory modality, the TEE images were recorded on different videotapes and blinded with random numbers for off-line analysis for determination of RV volumes and to calculate RV ejection fraction (EF) and RV SV. Simultaneously, ECG lead II and the arterial BP curve were recorded to document heart rate (HR) and invasive mean arterial blood pressures (MAP). Additionally, arterial blood gases (PaO_2 and $PaCO_2$) were analyzed in each patient after 10 minutes of conventional ventilation (control) and after another 10 minutes of SHFJV.

Right ventricular volumes were calculated according to the modified Simpson's rule method of discs as recommended by the American Society of Echocardiography, requiring only one mid-esophageal ventricular view.[12] With this approach, the RV chamber at end-diastole and end-systole is divided into a series of slices of equal thickness. The volume is calculated according to the following formula[13]:

$$\text{RV volume} = (\pi/4)\ \Sigma\ D\ (L/20) \qquad (1)$$

where L = height of the chamber, 20 = number of slices, and D = minor axis (slices) dimensions.

Right ventricular SV and EF were calculated according to the standard ventriculographic formulae for LV TEE-determined volumes:

$$\text{RVSV} = \text{RVEDV} - \text{RVESV} \qquad (2)$$

$$\text{RVEF}\ (\%) = \frac{(\text{RVEDV}) - (\text{RVESV})}{\text{RVEDV}} \qquad (3)$$

where RVSV = RV stroke volume, RVEDV = RV end-diastolic volume, RVESV = RV end-systolic volume, and RVEF = RV ejection fraction.

All determinations of chamber volumes were made with the software provided by the echocardiography machine (Hewlett-Packard Sonos 1500). For these calculations, measurements of the consecutive cardiac beats during one complete respiratory cycle (i.e., 6 seconds) were averaged. Statistical analysis of the normally distributed values was performed using the paired t test, and the data are expressed as means ± SD. A p-value less than 0.05 was considered statistically significant.

Results

The results are presented in *Table 1*. In 3 of the 20 anesthetized patients, echocardiographic measurements could not be performed because of the inability to define the RV endocardial border. The remaining 17 patients showed no statistical significant differences in RV systolic and diastolic volumes, EF, and SV, during the two modes of ventilation. The interventricular septum did not show any abnormalities in motion. In contrast, the interatrial septum demonstrated momentary mid-systolic bows toward the left atrium in 9 of 17 patients (53%) during continuous PPV but in 15 of 17 patients (88%) during SHFJV. Heart rate and MAP remained unchanged during jet ventilation. However, SHFJV resulted in significantly higher PaO_2 values and decreased $PaCO_2$ values ($p < 0.001$) compared to continuous PPV. Complications secondary to SHFJV were not observed in any of the patients.

Table 1. Parameters of Ventilation, Hemodynamics, and Gas Analysis during Continuous Positive Pressure Ventilation (CPPV) and Superimposed High-Frequency Jet Ventilation (SHFJV)

	CPPV	SHFJV
PIP (cm H_2O)	18.9 ± 2.9	18.9 ± 2.9
V_T (ml)	699.5 ± 114.5	n.d.
$Pdrive_{HF}$ (bar)		0.78 ± 0.12
$Pdrive_{LF}$ (bar)		0.83 ± 0.16
HR (bpm)	62.7 ± 8.7	60.1 ± 7.8
MAP (mmHg)	62.3 ± 7.5	65.4 ± 8.1
RVEDV (ml)	76.4 ± 16.2	75.0 ± 13.4
RVESV (ml)	32.6 ± 7.3	31.8 ± 6.7
RVEF (%)	57.3 ± 3.6	57.7 ± 3.9
RVSV (ml)	43.8 ± 9.6	43.2 ± 7.9
PaO_2 (mmHg)	139.6 ± 26.2	169.0 ± 36.6*
$PaCO_2$ (mmHg)	38.3 ± 3.8	30.5 ± 5.5*

Note: Data are means ± SD.

HR = heart rate; MAP = mean arterial pressure; n.d. = not done; PaO_2 and $PaCO_2$ = arterial oxygen and carbon dioxide tensions; $Pdrive$ = driving pressure of high-frequency (HF) and low-frequency (LF) jet streams; PIP = peak inspiratory airway pressure; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVSV = right ventricular stroke volume; V_T = tidal volume.

*$P < 0.001$.

Discussion

Transesophageal echocardiographic evaluation has become a most valuable tool for many indications perioperatively.[14] Previous studies have examined hemodynamic parameters in dependence of artificial ventilatory support and have shown the impact of ventilation and intrathoracic pressures on RV and LV preload and RV afterload.[15] However, assessment of the RV by two-dimensional echocardiography remains a challenge. The cavity exhibits a complex geometry. The ventricle and its outflow tract, both contributing to the emptying of the cavity, appear anatomically as separate entities. Thus, the RV is both technically and conceptually more difficult to study quantitatively than the LV.[16] Gibson *et al.*[17] found that the normal end-diastolic RV area should be no greater than two-thirds that of the LV. It also has been reported that

tricuspid annular plane systolic excursion in the mid-esophageal four-chamber view correlates well with RV EF ($r = 0.92$).[18] However, based on an external reference system, this method fails to account for any base-to-apex motion of the entire heart as it contracts and will yield different results in proportion to the angle between the transducer and annular point of motion.

The most widely used method to determine RV volumes is the Simpson's rule method. By this method, the RV chamber is divided into a series of slices of equal thickness and volume is calculated according to a specific formula (Equation 1). Simpson's rule has been widely used in echocardiographic studies to determine RV volume.[15–22] However, it underestimated dimensions or correlated poorly with RV volume as measured by angiography[17] or nuclear imaging.[19] This finding is most likely due to difficulty in identifying the true long axis of the RV in either view, the failure to include the infundibulum, or poor endocardial definition in some cases. Interestingly, correlation with RV EF was much better in these studies as might be expected, presumably because any errors in measurements were systematic (i.e., present in both the diastolic and systolic volume determinations).

Other methods to calculate RV volumes, such as techniques using a pyramid with a triangular base and the crescentic method[20] modeling a cross-sectional area with the use of the arcs of two intersecting circles, defined by the RV free wall and the interventricular septum, raised criticism apart from their complexity. A different approach to estimate RV volumes is to calculate the total volume of both chambers and then subtract the combined volume of the LV cavity and the interventricular septum.[21] However, this attempt underestimated true RV volumes by 11% to 14%. So far, no generally accepted two-dimensional technique for calculating RV volumes has been introduced into routine echocardiographic examinations.

Using TEE, our approach allowed RV examination using the modified Simpson's rule method from a mid-esophageal position. Our observation of momentary mid-systolic end-expiratory interatrial septal reversal (bowing toward the left atrium) during conventional ventilation with PEEP is in agreement with other investigators.[23] The overall shape of the interatrial septum changes in accordance with the interatrial pressure gradient due to the difference between pulmonary capillary wedge pressure (PCWP) and central venous pressure. In patients with normal hemodynamics at end-systole, left atrial pressure generally exceeds right atrial pressure. At mid-systole there may be considerable variation in the direction and magnitude of this relation.[24] However, at normal preloads the increase in right-sided venous return relative to the left with expiration will cause mid-systolic reversal. Kusumoto *et al.*[23] found that the end-expiratory mid-systolic reversal appeared to be a powerful predictor of PCWP less than 15 mmHg under a variety of conditions seen in the operating room. Thus, our findings of momentary interatrial mid-systolic septal bowing to the left are compatible with normal hemodynamic conditions during HFJV.

Several studies have investigated the cardiovascular effects of HFJV in animals and humans. Otto *et al.*[25] compared the hemodynamic effect of monofrequent HFJV and conventional ventilation in dogs, whereas Myles *et al.*[10] studied patients undergoing lung transplantation; both studies found no difference in hemodynamics between the two ventilation modes. Chiaranda *et al.*[8] studied the hemodynamic effect of PEEP during HFJV and conventional ventilation in dogs, and Travese *et al.*[9] in cats. They found that HFJV was associated with significantly better cardiovascular function when compared with conventional ventilation at the same level of PEEP. However, the improvement in CO seen in these two studies may be associated with the use of lower mean airway pressure during HFJV. Therefore, it is likely that any advantage of HFJV is directly related to the extent of lowered mean airway pressure during HFJV.[26] This observation is supported by Sugihara *et al.*,[27] who found no differences between HFJV and conventional ventilation with respect to SV and CO. Our data are in agreement with the experimental animal study of Mikhail *et al.*,[28] and the clinical trial of Myles *et al.*,[10] who found no significant differences between conventional ventilation and HFJV with respect to SV and CO.

The triggering of HFJV by electrocardiogram (ECG) has been studied by several investigators to determine whether there is any improvement in CO when ventilation rate is synchronized to HR. Cardiac-cycle specific synchronization of HFJV has been reported to increase CO, based on a delay between ventricular contraction and the jet impulse in animals,[29] whereas other researchers failed to demonstrate a significant difference in cardiorespiratory parameters when comparing synchronous *versus* nonsynchronous HFJV in patients without heart failure.[30] The impact of ventilation and its consequent changes in intrathoracic pressure on cardiac performance is likely to be more pronounced in the presence of cardiac compromise by altering ventricular loading conditions.[31] Accordingly, the increase of intrathoracic pressure as a ventricular assist selectively applied during systole, maximally improved CO in patients with congestive cardiomyopathy.[32] In the present study on SHFJV, no ECG triggering device was used in healthy patients. However, it may be of interest to investigate this alternative method in patients having severe myocardial insufficiency.

Mechanisms of improved gas exchange during HF ventilation have been discussed to include enhanced diffusion[33] but they also may depend on the application of high gas flows and increased airway pressure. One major concern is related to the appropriateness of airway pressure monitoring in view of development of increased peripheral airway pressures due to gas trapping. We measured PIP and PEEP inside the tracheal tube downstream from the jet nozzles by means of a cannula of the jet adapter according to experimental flow and pressure examinations. The measurement of pleural pressure would have enhanced our study but it could not be considered in these patients because of the invasiveness of the technique. Similarly transmural pressure could not be determined because of interference with the esophageal

TEE probe. Therefore, we cannot rule out the generation of auto PEEP during HF ventilation above the PEEP levels measured as a cause of improved gas exchange.

The application of high amounts of dry gas and cooling of inspiratory gases at the jet nozzles due to the Joule-Thomson effect bears a high risk for lesions of the airway mucosa.[34,35] To avoid damage to the mucosa, we integrated a standard hot water humidifier into the bias flow and injected a heated 0.9% saline continuously to be nebulized and propelled by the HF jet stream. Using this humidification system, none of our patients complained of respiratory problems after short-term SHFJV. However, airway pathology has to be considered, and duration of long-term HFJV may be limited if warming and humidification of gases appear to be inadequate, as indicated by the macroscopic appearance of the tracheal epithelium. This may be of particular concern in patients with bronchopleural fistulae or pulmonary insufficiency who require long-term respirator treatment.

In conclusion, TEE imaging of the right heart did not show any significant difference after transition of ventilation to SHFJV performed at similar peak airway pressures and PEEP. Our results show that SHFJV is a safe and effective alternative mode of HF ventilation. Further studies will include patients with pulmonary insufficiency to examine whether this new technique improves gas exchange and allows a consequent reduction in airway pressure.

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Determination and quantification of clonidine in human blood serum

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Abstract

Clonidine ((2-[2,6-dichlorophenyl]amino)-2-imidazoline) preferentially stimulates central α_2-adrenoceptors, which leads to inhibition of sympathetic tone, resulting in a lowering of arterial pressure and of heart rate. Additionally, many other desirable and undesirable effects are described, including analgesia, sedation and withdrawal reactions, which consist of a sudden rise in arterial pressure, nervousness, agitation and increased heart rate.

The present study has the goal to develop a simple and effective method for the analysis of trace amounts of clonidine in human blood serum. Special emphasis is necessary to make application of electron impact ionization and separation of the analyte fragments in a quadruple mass analyzer suitable. The procedure comprises solid phase extraction followed by formation of the pentafluorobenzyl derivative. Further purification is achieved by phase transfer extraction into an acidic aqueous solution succeeded by re-extraction into dichloromethane. After solvent exchange, an aliquot is injected into the gas chromatograph equipped with a DB5 MS capillary column and a mass spectrometric detector. Chromatograms are recorded in single ion monitoring mode. Quantification is accomplished by internal standardization with moxonidine [4-chloro-5-(2-imidazolin-2-yl-amino)-6-methoxy-2-methylpyridine].

Keywords: Clonidine; Moxonidine; Pentafluorobenzylbromide; Gas chromatopgraphy; Derivatization

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1. Introduction

Clonidine ((2-[2,6-dichlorophenyl]amino)-2-imidazoline) is a potent drug, which is used since more than three decades in the treatment of arterial hypertension [1]. The interaction of clonidine with a group of central α-adrenergetic receptors is supposed to be the reason for lowering blood pressure [2]. The active agent is administered orally in tablets or in infusions as its hydrochloride, which is traded under the brand name "Catapresan", in a dose of 50 to 200 μg/day. Due to side effects, which are attributed to the oral uptake, transdermal therapeutic systems were developed [3]. Clonidine was also used for therapy of glaucoma, soothing of withdrawal syndromes of morphine addicts and as a prophylaxis against migraine. Within the last 10 years, clonidine moved again into the interest of medical research, due to the discovery of its strong analgesic property [4]. Meanwhile, it is investigated towards its analgesic, respectively anxiolytic, effects in premedication of various surgeries [5,6]. A promising application is the local administration at the place of operation. The advantage of this form of medication is that the cardiovascular system is a priori not strained by the active agent. Therefore, undesirable side effects should be reduced. Presently, the analgesic effect of Catapresan at intra-articular dosage after athroscopic knee operations is investigated. The transition rate of clonidine of the knee joint into blood is supposed to be very low. Even at oral or intravenous administration of the mentioned dose, analyte concentration is in the range of nanogram to picogram per millilitre plasma [7]. For that reason, sensitive methodologies are required for the determination of the drug in human body fluids.

A variety of methods has been reported including radio immunoassay (RIA) [8], high performance liquid chromatography [9] and gas chromatography [7,11–14]. The deficiency of the liquid chromatography/UV-detection procedures is the lack of sensitivity. Limits of detection were in the microgram per millilitre range [10]. Gas chromatography showed to be more effective, but sample preparation is more laborious. Generally, separation of the analyte from the complex matrix and enrichment is inevitable. This is preferably done by solid phase extraction on octadecyl-cartridges [11]. Solvent extraction of alkaline plasma samples is described too [12]. In order to enhance gas chromatographic properties of the target compound, the secondary amino groups of the imidazoline function are derivatized to tertiary amines or amides [7,13]. Further purification is necessary to remove excess reagent. Concentrated samples are injected into the gas chromatograph either by on-column or splitless injection. Analyte detection is accomplished mainly by mass spectrometry. The most dominant ionization method for this analysis purpose is negative chemical ionization. Recording the chromatograms in selected ion monitoring mode gives high selectivity and sensitivity [11]. Electron capture detection was also used for the measurement of perfluoro-derivatives of clonidine [14]. Quantification was generally accomplished by the method of internal standardization. Deuterated clonidine-D_4 molecules as well as other imidazolines with similar structure were used as internal standards.

The task of the present work was to develop a method for the measurement of low levels of clonidine in human blood serum, to control the concentration of clonidine in serum after a single intravenous dosage, which was done at half of the test persons, respectively to elucidate the transference rate from intra-articular administered drug into

the cardiovascular system of the other part of patients. Special regard was set to widespread applicability, which implied analysis with standard instrumentation. The developed method is critically discussed and compared with previously published sample treatments. Limits of detection and quantification are evaluated by means of statistical methods.

2. Materials and methods

2.1. Chemicals and reagents

Clonidine was purchased as its hydrochloride from Fluka (Buchs, Switzerland), the quality was better than 98%, while moxonidine [4-chloro-5-(2-imidazolin-2-yl-amino)-6-methoxy-2-methylpyrimidine], which was used as internal standard, was thankfully supplied by Eli Lilly Company (Indianapolis, IN, USA). Water was prepared with a Barnstead Nanopure Ultrapure Water System from International PBI (Milan, Italy) and IKA distillation unit (Janke&Kunkel, IKA Labortechnik, Staufen, Germany). Methanol picograde, acetone picograde and dichloromethane (for HPLC) were obtained from Promochem (Wesel, Germany). Potassium dihydrogenphospate (pro analysis) and potassium hydroxide (pro analysis) as well as absolute ethanol (pro analysis) were delivered from Merck (Darmstadt, Germany). Dimethyldichlorosilane with purity better than 98% and di-sodiumhydrogenphosphate (free of water) were purchased from Fluka. The derivatization reagent pentafluorobenzylbromide was obtained from Sigma-Aldrich (Vienna, Austria). Toluene was ordered in the quality Ultra-Resi-analyzed at Baker (Phillipsburg, NJ, USA).

2.2. Preparation of standards and reagents

For calibration purposes, the method of internal standardization has been applied. Standards were prepared by appropriate dilution of concentrated stock solutions of clonidine hydrochloride (523 μg/ml) and moxonidine (506 μg/ml). The active agent was dissolved in 10 ml of a mixture of acetone and 5% (v/v) triethylamine, while pure acetone was used for dissolution of moxonidine. Standards were prepared in distilled water as well as in pooled blank serum. Analyte concentrations between 44.9 and 371 pg clonidine and 5.06 ng moxonidine/ml were used for calibration purposes. The pH-value of the standard solutions was adjusted to about 12 by addition of potassium hydroxide solution.

Standard volumes up to 100 μl were handled by means of calibrated capillaries (Brand, Wertheim/Main, Germany), while the derivatization reagent and organic solvents were transferred with adjustable Transferpettors (Brand). Aqueous sample volumes were pipetted with fixed volume Transferpettes (Brand).

Dimethyldichlorosilane was used in a concentration of 5% (v/v) in toluene for deactivation of glassware.

The buffer solution (pH = 7) was prepared by weighing 1.76 g potassium dihydrogensulfate and 3.63 g of disodium hydrogenphosphate into a 100-ml volumetric flask, which was filled up to the ring mark with distilled water after dissolution of the salts.

2.3. Solid phase extraction

OASIS™ HLB extraction cartridges with an adsorbent quantity of 60 mg were purchased from Waters (Vienna, Austria) and were preconditioned prior to sample adsorption with 2 ml of methanol and 2 ml of alkaline, aqueous solution (pH = 12). One millilitre of a standard solution was pipetted onto the extraction cartridge, followed by rinsing of the cartridge with 2 ml of alkaline water. For the removal of excess water, the cartridges were centrifuged (Z510, Hermle, Germany) at 90 × *g* for 3 min and purged with dry air through the adsorbent bed for a period of 20 min. For this purpose, as well as for the loading of the cartridges, a Baker SPE 12G solid phase extraction unit was applied. Analyte elution was accomplished with 1.5 ml of methanol. The eluate was collected in a deactivated 4 ml glass vial, which was tightly sealed with a PTFE-butylrubber septum in a screw cap.

2.4. Derivatization

The imidazoline function needs to be derivatized in order to enhance volatility and chromatographic properties. This was achieved by the reaction of the target compounds with pentafluorobenzylbromide (Fig. 1). The reaction solution was prepared by blowing first the methanolic sample extracts to dryness in a gentle stream of nitrogen and reconstitution of the residue in 1 ml of toluene. Fifty microlitres of triethylamine were added to guarantee alkaline conditions. The derivatization reaction was initiated by addition of 200 µl of the pentafluorobenzylbromide solution (5% (v/v) in toluene) and kept at 65 °C overnight.

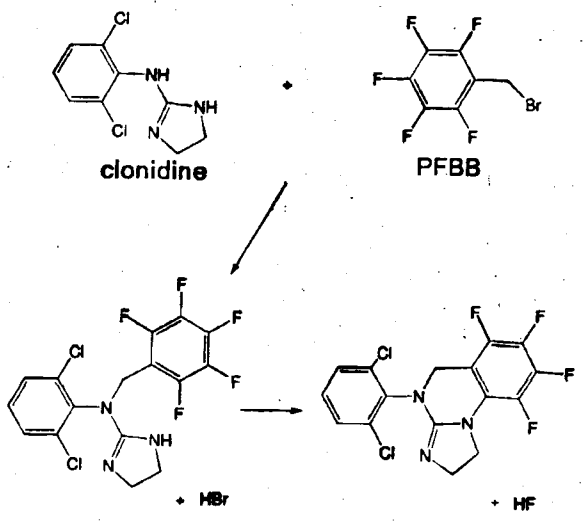

Fig. 1. Reaction of clonidine with pentafluorobenzylbromide.

2.5. Clean up

The derivatives were isolated by phase transfer extraction into 2 ml sulphuric acid (0.3 M). The organic phase was withdrawn and the aqueous solution was extracted again with a 1-ml aliquot of toluene. After removal of the toluene, the pH-value of the aqueous solution was adjusted by the addition of 300 μl of a 5-M potassium hydroxide solution to about 12. Additionally, 10 μl of *n*-butanol was added to prevent adsorption of the derivatives on the surface of the vial. The analytes were extracted as their free bases into 1 ml of dichloromethane and the aqueous phase was discarded. Excess KOH was removed from the dichloromethane phase by first extracting it with 2 ml of the pH 7 buffer solution, followed by extraction with 1 ml of distilled water. Finally, 30 μl of toluene were added and the volume of sample was reduced to about 100 μl and transferred into deactivated 100 μl micro inserts for 2 ml auto injector vials. Further reduction of the solvent volume (to about 30 μl) was achieved by a gentle stream of inert gas.

All extractions were performed for a period of 3 min by the use of a Heidolph Vortex vibratory mixer (Heidolph, Gobheim, Germany) and phase separations were accomplished by centrifugation of the samples for 2 min at $90 \times g$. Aliquots of 2 μl were injected for gas chromatographic analysis.

2.6. Instrumentation and conditions of analysis

A Hewlett Packard 6890 gas chromatograph was equipped with a HP 7683 automatic injector, a split/splitless injection port and connected to an Hewlett Packard 5973A mass selective detector (Hewlett Packard, Wilmington, DE, USA). The derivatives were separated on a DB 5 capillary column (J&W Scientific, Folson, CA, USA), 30-m length, 0.25 mm internal diameter and 0.25 μm film thickness. Target analytes were ionized by electron impact ionization at 70 eV and detected in single ion-monitoring mode. Together with the most characteristic fragment ions, one qualifier fragment was recorded for each compound simultaneously to check for potential interferences. This could be accomplished automatically during data analysis by calculation of the ratios of the abundance of the target ion signals to the qualifier ion signals. Target ions had a mass to charge ratio (m/z) of 354 for clonidine and 366 for moxonidine, while $m/z = 356$ in the case of clonidine, respectively $m/z = 401$ for moxonidine were recorded as qualifier ions. Data acquisition was carried out with a G1701BA Hewlett Packard MS ChemStation, version B.00.00. The injection port of the gas chromatograph was operated at 270 °C. A pulsed splitless injection with a pulse pressure of 100 kPa for 1.0 min was selected. The oven temperature program was chosen as follows: 70 °C for 1.0 min, 25 °C/min to 200 °C for 0 min, and 10 °C/min to 300 °C for 1 min.

3. Results and discussion

3.1. Reduction of adsorption phenomena

During the course of sample preparation, special care has to be taken to avoid adsorption of the analytes on raw glass surfaces. Therefore, all glassware was deactivated

by silylation with dichlorodimethylsilane as has been described elsewhere [15]. Nevertheless, some possibility of adsorption due to residual hydroxyl groups on the inner surface of the vials may remain. For the analysis of amines, further reduction of adsorption phenomena was attained by the addition of small amounts of an alcohol to the samples [15]. In the present study, *n*-butanol and triethylamine were added to the sample to displace the derivatives from the adsorption positions.

3.2. Differences compared to already published methods

The application of OASIS™ HLB-cartridges, which contain a special copolymer as adsorbent, allows to increase the pH-value above the pK_a value of clonidine, in order to shift equilibrium towards the free basis. Thus, the adverse effect of partial hydrolysis of the adsorbent, which could happen with the application of silica base C18-material, can be prevented.

In previously published methods, clonidine was analyzed as its di-trifluoromethylbenzoyl- or pentafluorobenzoyl-derivative [7,11,13]. In this work, pentafluorobenzylbromide (PFBB) was chosen as a reagent offering the advantage of a lower molecular weight of the resulting amines compared to those of the diamides, which are formed in reactions with the specified acyl bromides. The better volatility of the derivatives allows an analysis under more moderate conditions.

Instead of acetone, which has been proposed by Yamahata et al. [11], toluene was chosen as solvent for the derivatization step. The higher boiling point of toluene diminishes the risk of solvent losses during the reaction period. Potassium carbonate, which had been used to catch the hydrogen bromide and hydrogen fluoride [14], has the disadvantage of insolubility in the reaction mixture. Since the solution formed two phases and was not further agitated, improper removal of the reaction by-products could occur. For this reason, the inorganic salt was replaced by addition of the strong organic base triethylamine, which provides for a proper reaction environment due to a pK_a value of about two units higher than that of clonidine.

A further modification concerns the solvent used for re-extraction of the sample components for clean up purposes. In contrast to all of the previously published methods, which proposed solvents with a density lower than water, dichloromethane was used for this purpose in this work. This solvent permits for an ease of phase separation and the glass tubes need not be changed for discarding the aqueous layers. As a result, improved precision can be observed.

3.3. Statistical evaluation of the method

Aqueous standards were applied for method development. The established procedure was evaluated by measurement of spiked serum samples. Recovery from the serum samples was between 70% and 80%, which indicates strong matrix effects. Therefore, internal standardization is absolutely necessary. Blank values of the pooled serum, which was used for sample preparation, were found to be below the limit of detection. At least four replicate samples were measured for calibration purposes at nine concentration levels between 45.1 and 375.5 pg/ml serum. Due to the laborious sample preparation, calibration

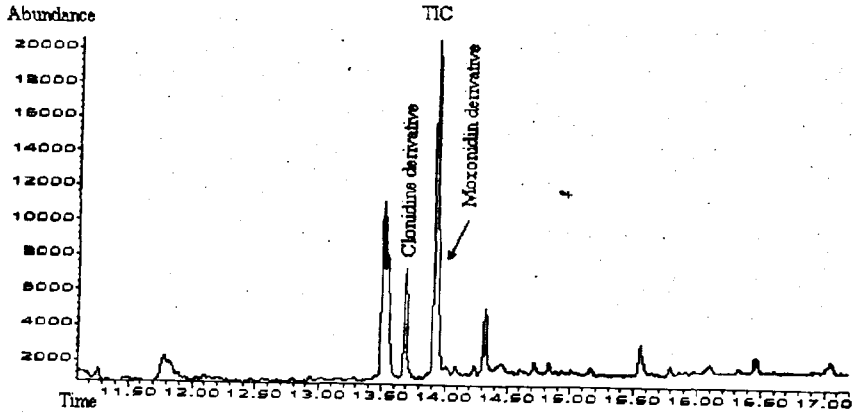

Fig. 2. Representative total ion chromatogram (TIC) of a spiked serum sample containing 228 pg/ml clonidine and 5.06 ng/ml moxonidine.

standards were prepared at three consecutive days. A representative total ion chromatogram of a sample containing 228 pg/ml of clonidine is depicted in Fig. 2. Integration was accomplished by an automatic routine. Additionally, all chromatograms were checked for proper integration settings.

As can bee seen easily, the applied clean up and measurement procedure has proved to be suitable for selective isolation of the derivatives. Analyte peaks are clearly separated from potential interference. For identification of the peaks eluting with retention times close to the analytes, measurements were performed by operating the instrument in full scan mode. The peak eluting in front of clonidine was identified as cholesterol. The peak, which is eluting immediately after clonidine, could not be reliably identified, due to its low intensity. Raw data of the spiked serum samples were used for the determination of the first order calibration graph and the limit of detection of the method. Calculation was performed according to Eurachem guide with the software "ValiData Excel-Makro zur

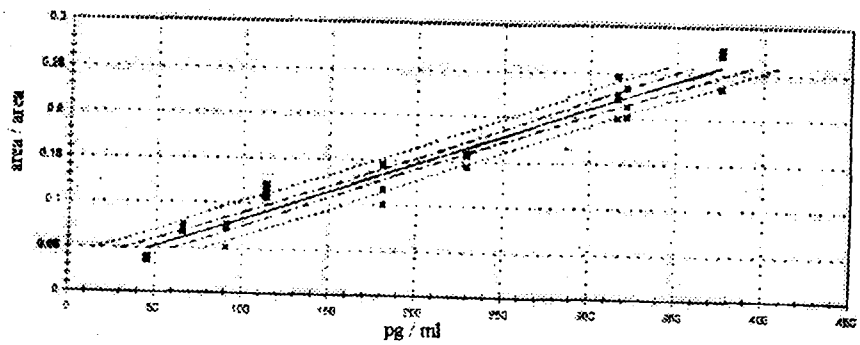

Fig. 3. First order calibration graph of the measurements of clonidine in human blood serum.

Methodenvalidierung, Wegscheider, Rohrer and Neuböck, Version 3.02.54 ger" at the 95% confidence interval [16]. Fig. 3 shows the resulting calibration graph, including the limits of the 99% respectively 95% confidence region. The limit of detection for clonidine was determined with 26.3 pg/ml and limit of quantification with 87.5 pg/ml serum sample. The coefficient of variation of the method was calculated with all calibration data and found to be 13.8%. Thus, the method is suitable to detect even the low amounts of clonidine, which are expected in human blood serum after a single intravenous, respectively, intra-articular administration of 150 μg of the drug.

4. Concluding remarks

The goal of the present study was the development of a method for the determination of clonidine in human blood serum by application of electron impact ionization and separation of the analyte fragments in a quadruple mass analyzer. The procedure consists of a solid phase extraction on a polymeric adsorbent followed by formation of the pentafluorobenzyl derivatives, which are purified by phase transfer extraction. After solvent exchange, the toluene solution is injected into the gas chromatograph equipped with unipolar capillary column. Statistical evaluation of the applied sample preparation and analysis procedure has shown that the described method is suitable for this analytical task. Hence, this method will be applied for the evaluation of a clinical study, which concerns the pharmacokinetic properties of intra-articular administered clonidine.

Acknowledgements

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INTRAVENOUS MELATONIN REDUCES THE DEMAND FOR PROPOFOL DURING GENERAL ANAESTHESIA

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Running head: Melatonin reduces propofol demand

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SUMMARY

A total of 40 healthy patients, undergoing eye surgery, were randomly assigned to receive either total intravenous anesthesia with propofol following a single bolus dose of 1 mg melatonin or placebo 15 minutes before induction of anesthesia. Propofol consumption in every patient was evaluated for at least 30 minutes and up to 90 minutes every 5 minutes after induction of anesthesia. Propofol demand was lower in the melatonin group compared with placebo (113 ± 10.8 µg kg^{-1} min^{-1} vs. 124 ± 12.7 µg kg^{-1} min^{-1}, p=0.046). Time to loss of consciousness, propofol dose during induction and hemodynamic parameters did not differ between the groups (Table 2). No adverse events were observed perioperatively. We conclude that premedication with melatonin reduces the amount of propofol required for anesthesia, but the magnitude of this effect may be too small (<10 %) to be of advantage compared with patients receveing other premedicants.

Keywords: melatonin, propofol, praemedication, anaesthesia.

INTRODUCTION

Melatonin (5-methoxy-N-acetyltryptamine) is a key regulator of the circadian rhythm of sleep-wakefulness. It is synthesized in the pineal gland (1;2) under neurological inputs from the suprachiasmatic nucleus (SCN) of the hypothalamus and is regarded as the biological clock in mammals (3). This highly lipophilic pineal hormone is associated with the regulation of day/night-dependent physiological processes such as sleep, reaching its maximum plasma levels during night time. Sublingual administration of melatonin has been shown to be similar effective as midazolam to reduce anxiety and to increase sedation but without the psychomotor impairment of benzodiazepine derivates (4;5).

Therefore, we assumed that melatonin might be of use in the induction and maintenance phases of anesthesia with propofol. We investigated whether intravenous melatonin, given 15 minutes before induction of anesthesia, may have a propofol-saving effect using an automated intravenous target controlled infusion (TCI) system (6;7).

METHODS AND RESULTS

After approvement by the institutional ethics committee and written informed consent, 40 patients admitted for day case eye surgery, ASA physical status I - III, were randomly assigned by using a computer program to receive either 1 mg melatonin (n = 20) or placebo (n = 20), 15 minutes before induction of anesthesia. Melatonin- and placebo-solutions were freshly prepared by the local pharmacy and were administered in a double blind fashion. Patients did not receive any other premedication. Surgery was performed between 8 a.m. and 1 p.m. Monitoring included ECG, oxygen saturation, endtidal CO_2 and non-invasive blood pressure measurements. Pure oxygen (100%) was administered for at least 3 minutes before induction. According to patient weight and age, a propofol TCI syringe pump (Diprifusor™ Master TCI, Becton Dickinson, NJ, USA) was set to achieve a plasma propofol level of 8 $\mu g\ ml^{-1}$ during an infusion time of 3 min. Simultaneously, a continuous infusion of 1 $\mu g\ kg^{-1}\ min^{-1}$ remifentanil was started. After 1 min the infusion rate was reduced to 0.1 $\mu g\ kg^{-1}\ min^{-1}$ and vecuronium 0.1 $mg\ kg^{-1}$ was administered. During initiation of the induction phase, the patients were asked to open their eyes and to take a deep breath every 10 seconds. Failure to respond to three consecutive commands and absence of the lid reflex was considered as loss of consciousness (LOC). The cumulative dose of propofol and the delivery rate was documented automatically by the TCI device every 5 minutes. After ventilation with a mask the trachea was intubated after another 3 minutes. Patients were ventilated with an oxygen-air mixture and anesthesia was maintained with propofol with the Diprifusor's infusion rate adjusted to maintain normal heart rate and blood pressure within a 20% interval from baseline values determined as mean from three

measurements performed within 18 hours preoperatively. Blood samples were taken to assess melatonin plasma levels before, 30 minutes and 75 minutes after induction of anesthesia via a standard radio immuno assay (RIA, Bühlmann Laboratories AG, Allschwil, Switzerland).

Data from 36 patients were evaluated, data of 4 patients of the melatonin group could not be assessed because of a lost TCI pump. Morphometric and hemodynamic data were comparable within both groups (Table 1). Likewise, time to LOC (121.6 ± 25.3 sec *vs* 135.4 ± 30.7 sec, n.s.) and propofol dose during induction (120.4 ± 33.2 µg kg^{-1} min^{-1} *vs* 129.7 ± 34.7 µg kg^{-1} min^{-1}, n.s.) were similar thus being not affected significantly by melatonin. Following melatonin administration, melatonin plasma levels reached 5672 ± 1762 pg/ml (mean, SD) within 30 minutes and 3400 ± 1567 pg/ml within 75 minutes after induction of anesthesia *vs* 1.9 ± 3.7 pg/ml and 1.5 ± 2.1 pg/ml in the placebo group, respectively ($p<0.0001$).

However, propofol consumption was lower in the melatonin group compared with the placebo group (Figure 1). No adverse events were observed perioperatively.

COMMENT

In this study we showed that exogenous administration of melatonin could reduce the demand of propofol during anesthesia. However, this effect was neither associated with a decrease of propofol requirement during induction of anesthesia, nor with a shortening of time to loss of consciousness. Although recent comparisons of melatonin with midazolam showed that melatonin can decrease anxiety levels and increase levels of sedation without impairment of postoperative cognitive and psychomotor skills (5), the propofol saving effect studied in our patients was small. Contrarily, midazolam premedication has been reported to reduce propofol dose requirements > 10 % for various anesthetic endpoints (7). While melatonin does not seem to be a substitute for midazolam, the combination of both substances might be useful in reducing anesthetic requirements and undesirable side effects and should be evaluated in further studies.

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Title: TWO DIFFERENT DOSES OF INTRATHECAL CLONIDINE FOR LABOR ANALGESIA

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Introduction: Intrathecal (i.t.) clonidine produces a dose-dependent analgesia in the postoperative setting, accompanied by hemodynamic depression (1). The aim of our study was to compare two different doses of i.t. clonidine for labor analgesia with respect to analgesia as well as side effects.

Methods: After IRB approval and written informed consent 23 parturients were randomly assigned to receive i.t either 100 µg clonidine (C100) or 200 µg clonidine (C200) via a combined spinal-epidural needle. Labor pain was assessed using a visual analog scale (VAS: 0-10) prior to i.t. drug administration, thereafter in short intervals until request for epidural local anesthetic. Hemodynamics as well as cardiovascular drug support with ephedrine were also recorded. For statistical evaluation ANOVA was used. A P-value < 0.05 was considered significant.

Results: Doubling the clonidine dose resulted in comparable duration of analgesia but significantly increased quality of analgesia. In the C200 group, hemodynamic depression required treatment with ephedrine significantly more often (Table 1).

GROUP	C100 (N=13)	C200 (N=10)
Duration of analgesia (min)	126 (±20)	132(±13)
Max pain relief (Δ % VAS) of baseline	64 (±8)*	83 (±6)
Number of patients receiving ephedrine	1/13*	8/10

Table 1: Values are mean (±S.E.M.), * $P < 0.05$ vs. C200

Conclusion: Although 200 µg of i.t. clonidine produced more profound analgesia than 100 µg, we recommend close hemodynamic monitoring as cardiovascular depression might be more pronounced as well.

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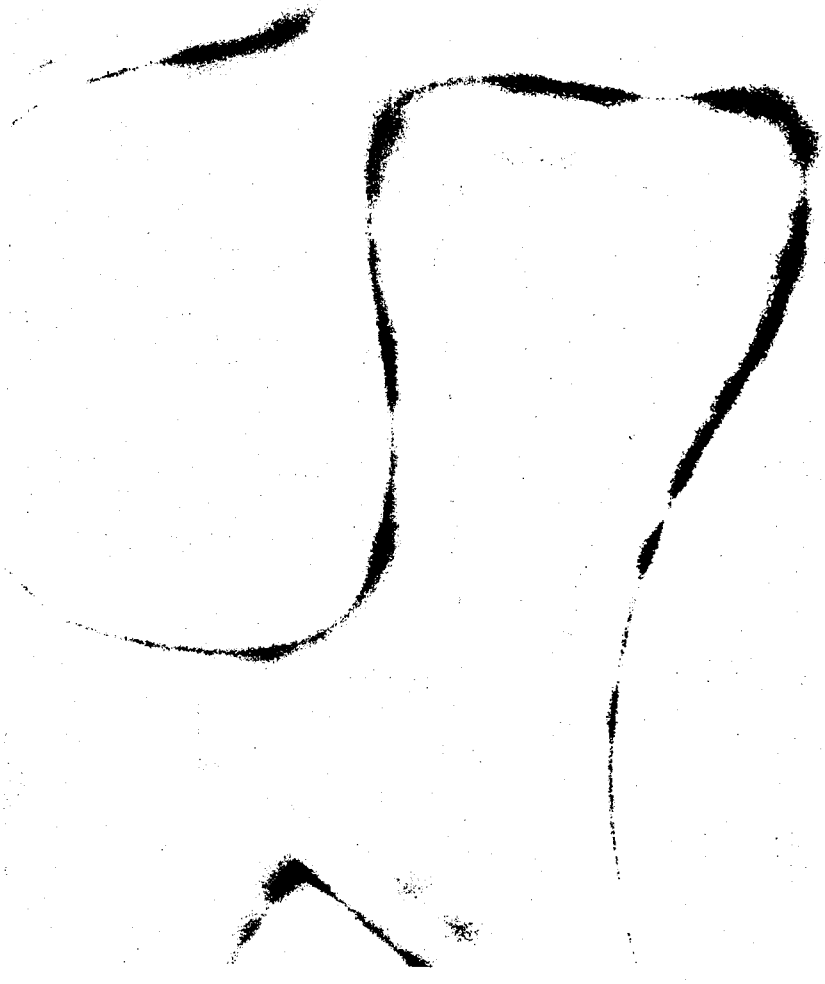

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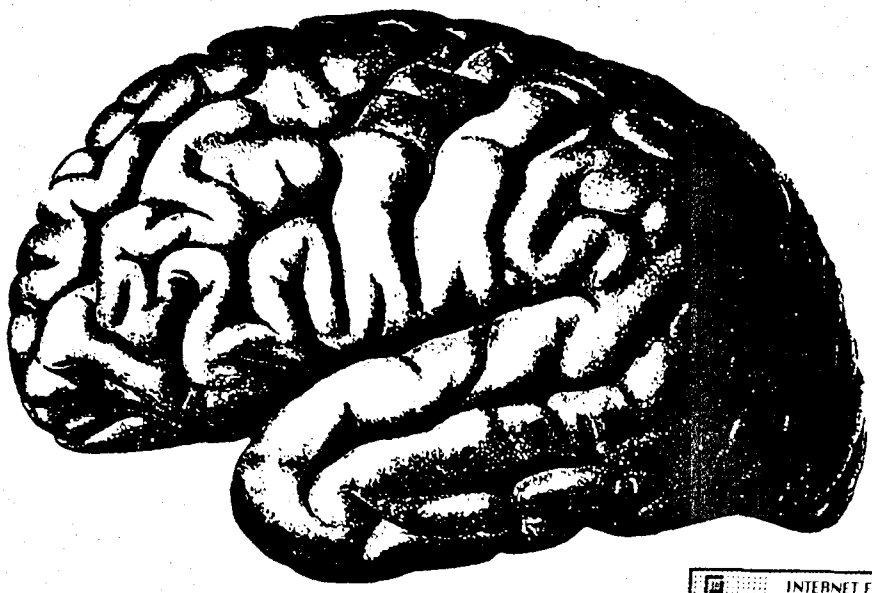

INTERNET FÜR ALLE!

Testen Sie jetzt 10 Stunden den Internet-Zugang bei Netway für nur öS 50,-. Anruf genügt!

Was man nicht im Kopf hat, sollte man im Internet haben.

Man schätzt, daß rund 80 Prozent des Wissens der Menschheit im Internet abrufbereit ist: Im Gesundheitsbereich sind das medizinische Datenbanken und Informationsnetzwerke ebenso wie die bedeutendsten Fachzeitschriften oder weltweit führende Forschungsinstitute. NETWAY bietet Ihnen als einer der führenden Internet-Anbieter Österreichs nicht nur vollen Internetanschluß, sondern auch Beratung, zahlreiche Zusatzangebote und eine ständige Service Hotline. Schon ab internette öS 277,-/Monat.

Netway AG:
Hollandstraße 11-13, A-1020 Wien
Tel.: 01 217 19-100,
Fax: 01 217 19-199
email: info@netway.at,
www.netway.at

KURIER ONLINE

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Köpfchen!

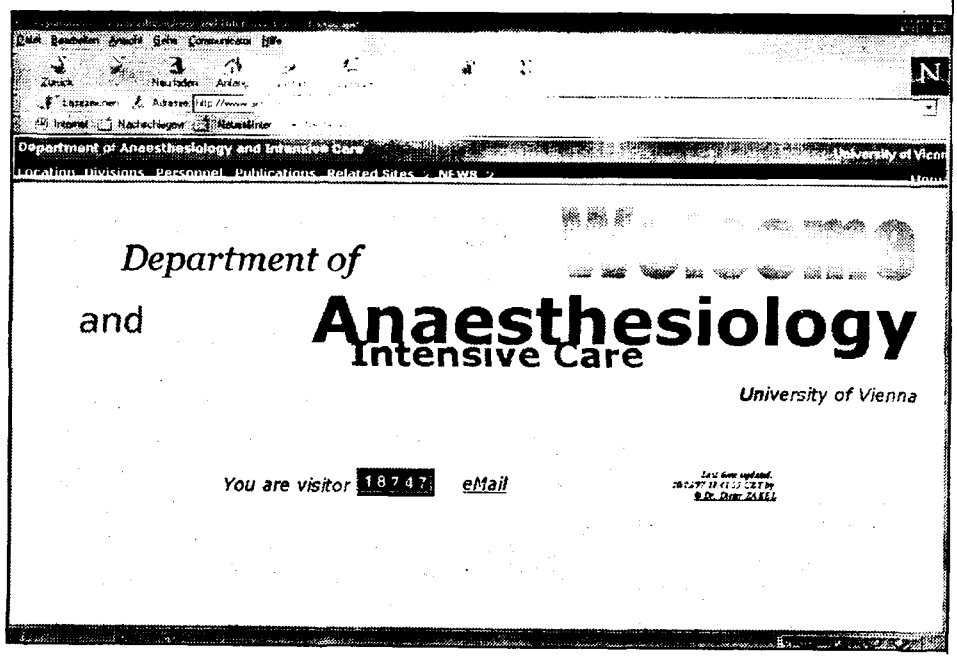
Netway ist Provider des Kurier-Online

Die Anästhesie und Intensivmedizin sind Pioniere des Internet im klinischen Bereich. Schon Anfang der 90er Jahre, als der erste Internetanschluß in Österreich durch die Universität Wien verwirklicht wurde, schossen die Anästhesie-Server wie Pilze aus dem Boden.

Zum jetzigen Zeitpunkt stehen in Österreich ungefähr 40 Server, die sich nur mit diesem Fachgebiet befassen. Es sind öffenliche und private Server, teils mit akademischem, teils mit wirtschaftlichem Interesse im Hintergrund. Nicht immer lassen sich diese beiden Interessengruppen trennen, da die Verantwortlichen im akademischen Bereich aus Gründen des aktuellen Sparkurses eine enge Kooperation anstreben.

Eine unübersehbare Vielzahl an Dokumenten beschäftigt sich mit diesem Fachgebiet. Kein Wunder, ist es doch das umfangreichste in der Klinischen Medizin. Daher ist es auch nicht verwunderlich, daß Organisationen, Kliniken, Pharma- und Medizintechnikfirmen ihre Präsenz im Internet immer mehr forcieren.

Wenn man in den gängigen Suchmaschinen wie Altavista und Lycos oder auch Yahoo nach dem Begriff "Anaesthesiology" oder " Anästhesie" sucht, erhält man als Suchergebnis: "about 73400 documents match our query". Plus minus, versteht sich.



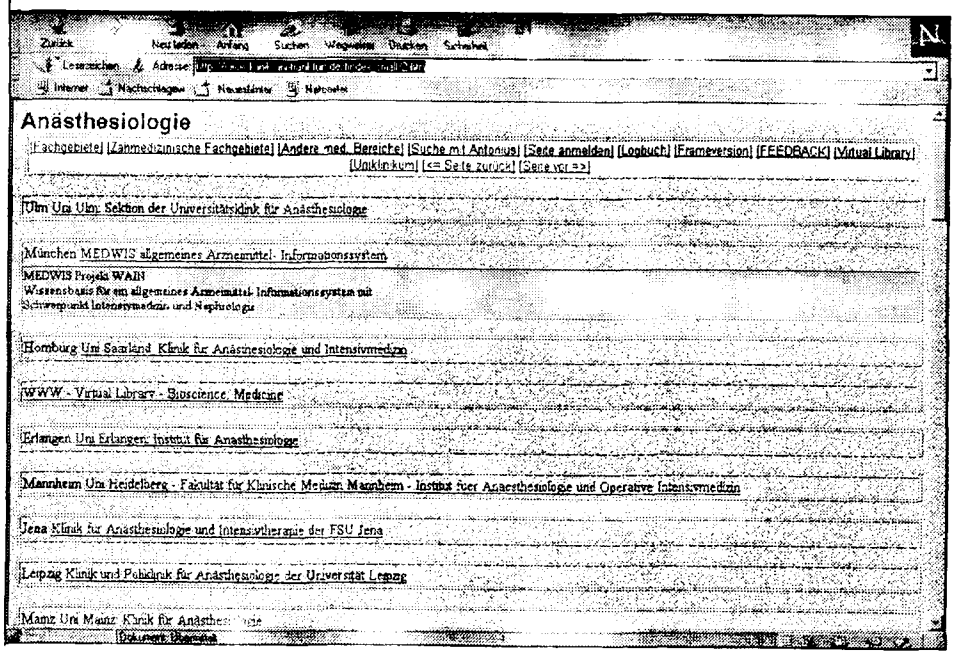
2. Die ÖGARI
(http://www.anesthesia.at/oegari.htm)
Österreichische Gesellschaft für Anaesthesiologie - Reanimation und Intensivmedizin.

3. Die DGAI, die Deutsche Fachgesellschaft, erreicht man unter (http://www.dgai.de/). Hier sind die aktuellen deutschen Links sehr übersichtlich zusammengestellt (http://www.klinik.uni-frankfurt.de/findex_small/2.htm).

4. Die ESS - die European Shock Society
(http://www.univie.ac.at/ESS)
beschäftigt sich europaweit mit der Erforschung des Schockgeschehens, seiner Aufklärung und therapeutischen Richtlinien für dessen Therapie.

JOURNALS UND PUBLIKATIONSMEDIEN IM INTERNET:

Am J Physiol 1996
(http://www.uth.tmc.edu/apstracts/1995/heart/toc.html)
Anaesthesiology
(http://www.anesthesiology.org/)
Annals of Thoracic Surgery
(http://www.elsevier.nl/estoc/publications/ store/5/00034975/)



British Medical Journal
(http://www.bmj.com/bmj/index.html)
Cardiovascular Surgery
(http://www.elsevier.nl/estoc/publications/store/9/ 09672109/)
JAMA
(http://www.ama-assn.org/journals/most/recent/issues/jama/toc.htm)
Journal of Emergency Medicine
(http://www.elsevier.nl/estoc/publications/store/9/07364679/)
Journal of the American Journal of Cardiology
(http://www-east.elsevier. com/jac/Menu.html)
New England Journal of Medicine
(http://www.nejm.org/)
PAIN
(http://www.elsevier.nl/estoc/publications/store/9/03043959/)
Resuscitation
(http://www.elsevier.nl/estoc/publications/store/2/03009572/)
The Journal of Clinical Anesthesia
(http://www.elsevier.nl/estoc/publications/store/0/09528180/)

Diese Journals liegen nicht im Volltext vor. Absicht der Herausgeber ist es, uns neugierig zu machen, um das Originaldruckwerk zu kaufen. Die meisten amerikanischen Sites der elektronischen Magazine oder Journals verstehen sich meist als Marketinginstrument für die gedruckten Fassungen.
Genauso verhält es sich mit den meisten anderen Sites. Man muß hier seine persönliche Auswahl nach einem Besuch auf der Homepage treffen - je nach Interessensgebiet und Bedürfnis. Jeder der Links spricht primär die eigene Krankenhausumgebung an und ist im Vergleich zu den oben genannten Adressen nicht nur der Information verschrieben.

Dr. Dieter Zakl

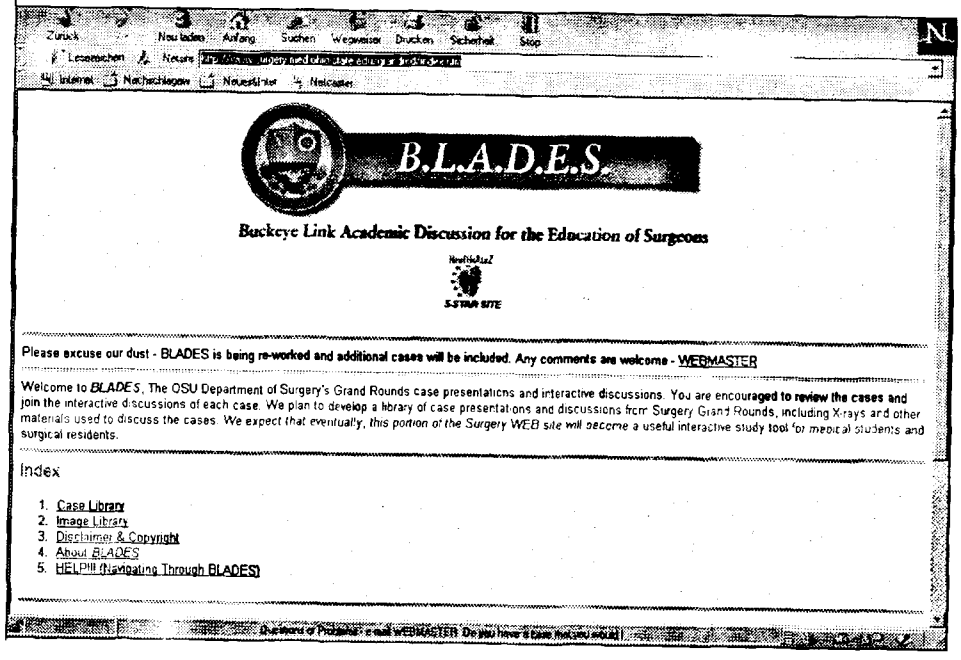
Chirurgie

Chirurgische Seiten im Internet gibt es genauso häufig wie für andere Medizinische Bereiche. Es ist aber sehr schwer mit den üblichen Suchmaschinen die richtigen sites' zu finden. Besser man sucht über auf Medizin spezialisierte Suchmaschinen (z.B.: Health from A to Z; Archie, Med Web, Med guide,..)

Prinzipiell findet man an allen medizinischen Universitätskliniken eigene chirurgische Adressen. Großen Wert wird gerade in Amerika auf die richtige Patientenaufklärung gelegt. Nurzu verständlich, wenn man von den horrenden Klagesummen und der Zahl der Klagen hört, die derzeit in den Vereinigten Staaten verhandelt werden.
Viele Universitäten besprechen auch die verschiedenen Operationstechniken, insbesondere werden lapraskopische Verfahren diskutiert.
Breiten Raum nehmen die Diskussionforen ein, die sich gerade in den USA großer Beliebtheit erfreuen.

Folgende chirurgische Fachbereiche wurden für diese Ausgabe untersucht:

* Allgemeine Chirurgie
* Plastische Chirurgie
* Pediatric surgery
* Cardiothoracic surgery



http://www.meddean.luc.edu/lumen/DeptWebs/peds/all-imm.htm
Allergy/Immunology Pediatric Consultation Guidelines
Disease categorized suggestions for appropriate clinical consultation. **Loyola.**

http://hiru.mcmaster.ca/cpg/sadb/acp/acptra01.htm
Allergy Testing Practice Guideline Abstracts
Disease categorized prototypes of structured abstracts.

http://www.pslgroup.com/dg/immuno.htm
Doctor's Guide Allergy & **Immunology Conferences**
Permits a search of an extensive medical conference database based on keywords, disease area, date or location.

http://www.immune.com/allergy
Allergy on LISTSERV: allergy discussion list.

http://www.healthtouch.com/level1/leaflets/104583/104583.htm
Healthtouch Allergy, Asthma Lung Disease Documents
Covers asthma, allergies, hay fever, colds, air pollution, and smoking.

http://www.med-library.com/docs/allergy.htm
Allergy Documents from MMRF
A specialty categorized index of pointers to internet disease documents for physicians, patients, and students. Multimedia Medical Reference Library.

http://allergy.mcg.edu/
Allergist's Patient Oriented Documents
Includes rhinitis and asthma patient handouts.

http://www.scienceXchange.com/aai/
American Association of Immunologists

Anästhesie

http://www.anesthesiaweb.com/
AnesthesiaWeb Monthly Magazine
Commentary and abstracts on current anesthesia practice, ambulatory care, critical care, and managed care. Free registration. Duke University Medical Center and Roche Laboratories.

http://www.pslgroup.com/dg/Anaesthesianews.htm
Anaesthesia News from Doctors Guide
Medical and pharmaceutical industry news, product announcements and research developments from conferences, journals, and newswires.

http://anaes.stjosephs.london.on.ca/
Anaesthesia Monitor Newsletter
University of Western Ontario.

http://www.anesthesiology.org/contents.html
Anesthesiology
Contains peer-reviewed materials from international investigators. A title is "Decreased Thiopental Requirements in Early Pregnancy." Searchable structured abstracts. American Society of Anesthesiologists.

http://www.hbuk.co.uk/wbs/aha/
Anaesthesia - Medical Journal
Provides current information on anatomy, physiology, pharmacology and pathology to help clinicians recognize potential complications of anaesthesia. Abstracts. W B Saunders Company Ltd.

http://biomednet.com/cgi-bin/members1/shwtoc.pl?J:ana
Current Opinion in Anaesthesiology
Offers expert updates on important clinical and research advances. BioMedNet Club. Selected abstracts. Fee membership for full text.$$

http://www.aaic.net.au/home.html
International Journal of Anaesthesia
Australian anaesthetic education updates and meeting reviews.

http://www.anesthesiaweb.com/
AnesthesiaWeb
Literature review, opinions, commentary and abstracts on current anesthesia practice, ambulatory care, critical care, and managed care. Free registration. Duke University Medical Center and Roche Laboratories.

http://gasnet.med.yale.edu
Global Anesthesiology Server Network
Includes information about the Anesthesiology discussion group,hypermedia anesthesia manuals, and abstracts of the Journal of Clinical Monitoring. Yale University.

http://www.asahq.org/
American Society of Anesthesiologists
Includes information about the organization, bylaws, standards, current publications and recent issues of the ASA Newsletter.

http://www.priory.co.uk/journals/anaes.htm
Anaesthesia On-Line International Journal
Gives new research information, news, and drug dosages and indications.

http://pharminfo.com/pubs/msb/msbana.html
Analgesic and Anesthetic Drug Reviews
Collection of articles that cover clinical uses, product releases and research developemt. An article title is "Caution Urged in Use of Sumatriptan." Pharmaceutical Information Associates, Ltd.

http://www.medana.unibas.ch/ENG/CIRS/Cirs.htm
Critical Incidents in Anaesthesiology
A list of critical incidents in anesthesia care from anonymous contributors to improve understanding among anesthesiologists. University of Basel.

http://www.eur.nl/FGG/ANEST/wright/
WWW World of Anaesthesia
A clickable map that provides access to global WWW anaesthesia resources.

http://www.mic.ki.se/Diseases/e3.html
Karolinska Disease Categories / Anesthesia
A systematic disease classification of Internet resources for laymen, health care professionals and scientists. Presented by a medical librarian team at Sweden's Karolinska Institute.

Dermatologie

http://www.newspage.com/NEWSPAGE/cgi-bin/walk.cgi/NEWSPAGE/info/d15/d8/d17/
Dermatology Daily News from Newspage
Articles relevant to this discipline from electronic newswires, newspapers, and trade periodicals. Abstracts. Registration for full text. Individual, Inc.

http://www.pslgroup.com/dg/dermanews.htm
Dermatologic Disorders News from Doctors Guide
Medical and pharmaceutical industry news, product announcements and research developments from conferences, journals, and newswires.

http://www.modernmedicine.com/derm/index.html
Dermatology Times
Offers topical disease categorized news briefs directed to the practicing dermatologist on STDs, cosmetic surgery, acne, practice management, etc.

http://www.chronicle.org/skin.htm
Chronicle of Skin and Allergy
Practical therapeutics and clinical news from the world of dermatology. Published monthly. Chronicle Information Resources Ltd. Canada.

http://matrix.ucdavis.edu/DOJ.html
Dermatology Online Journal
A peer reviewed dermatology journal that presents immediate access to new developments, original articles, and announcements.

http://link.springer.de/link/service/journals/00403/index.htm
Archives of Dermatological Research
Original papers cover new techniques and methods in experimental dermatology and the study of skin morphology and immunology.

http://www.ama-assn.org/journals/standing/derm/dermhome.htm
Archives of Dermatology
Publishes peer-reviewed articles. One of the oldest and most influential publications in its field. Covers therapeutics and clinical cases. Searchable abstracts and past issues. American Medical Association.

http://www.derm.ubc.ca/jcms/
Journal of Cutaneous Medicine and Surgery
Scholarly articles that reflect the state of the art in cutaneous biology and dermatology. An article title is "Infantile Myofibromatosis." Structured abstracts. Canadian Dermatology Association.

http://www.derm.ubc.ca/skintherapy/
Skin Therapy Letter
Detailed reviews of articles on treatment advances and new formulations reported at major dermatology meetings or from cinicians' experiences. International Skin Therapy Letter Inc.

http://www.mcphu.edu/libraries/resources/reviews/derm.htm
Dermatology Reviews for Primary Care
Disease and topical categorization of structured abstracts and reviews of important current articles from the world's premiere medical journals. Hahnemann University.

http://www.webmedlit.com/topics/DermLit.html
WebMedLit Dermatology Current Journal Articles
Presents topic categorized hyperlinked article titles recently posted to the web. Includes articles with abstracts and full text. Web Medical Literature Services.

http://www.telemedicine.org/WDS/newsletter1g.htm
Women's Dermatologic Society Newsletter
Articles provide a forum for professional development among women dermatologists.

http://www.cyberplex.com/ses/mediview/medi_derma_story.html
Medi-View Dermatology Reports
Full text reports from Canadian and international medical meetings.

http://www.telemedicine.org/IDS.htm
Internet Dermatology Society
This site offers membership information, templates for presenting case studies, online consultations, article abstracts, and Internet dermatology resource listings.

http://www.telemedicine.org/sidhome.htm
Society for Investigative Dermatology
Membership information, a description of programs and services from this national medical specialty society.

http://www.diabetes.org/DiabetesCare/
Diabetes Care Journal
Articles cover clinical trials, behavioral medicine, nutrition, education, health care delivery, medical economics, and clinical care. Includes a professional discussion forum. American Diabetes Association.

http://www.mcl.tulane.edu/classware/pathology/medical_pathology/endocrine_cases/casesTop.html
Case studies in Endocrine Disorders
Lectures, cases, and tutorials on endocrine pathology cover pituitary, thyroid, parathyroid, adrenal, and reproduction topics.

http://www.infowest.com/podiatry/medical/diabetic/diagnos/index.html
Diagnosing Diabetic Neuropathy
A set of photographs with accompanying text. The Center for Podiatric Information.

http://lib-sh.lsumc.edu/fammed/intern/dka.html
Diabetic Ketoacidosis Overview
A quick reference document. Louisiana State.

http://www.diabetes.org/internetresources.htm
ADA Diabetes Internet Resources
American Diabetes Association/Oregon.

http://www.lilly.com/diabetes/diabetes_education.html
Managing Your Diabetes Patient Program
Detailed patient instruction regarding issues such as sick day rules, traveling with insulin, etc. Eli Lilly and Company.

http://islet.medsch.wisc.edu/
Diabetes Knowledgebase
Provides diabetes related information. It includes patient oriented documents such as a diabetes dictionary and diabetes statistics. University of Wisconsin.

http://islet.medsch.wisc.edu/index.htm
Diabetes Information WWW server