Original Article

Wien Klin Wochenschr (2004) 116/9–10: 310–317


wiener klinische wochenschrift
the middle european journal of medicine
Printed in Austria

# High-dosage continuous amiodarone therapy to treat new-onset supraventricular tachyarrhythmias in surgical intensive care patients: an observational study

**Andreas J. Mayr**[1], **Martin W. Dünser**[1], **Nicole Ritsch**[1], **Werner Pajk**[1], **Barbara Friesenecker**[1], **Hans Knotzer**[1], **Hanno Ulmer**[2], **Volker Wenzel**[1], and **Walter R. Hasibeder**[1]*

[1] Division of General and Surgical Intensive Care Medicine, Department of Anesthesiology and Critical Care Medicine, and [2] Department of Medical Biostatistics, Leopold-Franzens-University, Innsbruck, Austria

**Hochdosierte kontinuierliche Amiodaron-Therapie zur Behandlung neu aufgetretener supraventrikulärer Tachyarrhythmien bei chirurgischen Intensivpatienten: eine Observationsstudie**

**Zusammenfassung.** *Ziel:* Neu aufgetretene supraventrikuläre Rhythmusstörungen (SVRS) stellen eine Komplikation dar, die wesentlich zur Morbidität und Mortalität von chirurgischen Intensivpatienten beiträgt. Obwohl nur wenige Daten über Effektivität bekannt sind, werden Klasse III Antiarrhythmika häufig zur Therapie neu aufgetretener SVRS bei chirurgischen Intensivpatienten verwendet.

*Studienort:* Allgemeine und chirurgische Intensivstation mit 12 Betten in einem Universitätslehrkrankenhaus.

*Design:* Retrospektive Observationsstudie.

*Patienten:* 131 chirurgische Intensivpatienten mit SVRS (Nicht-Sinus Schmalkomplextachykardie mit Herzfrequenzen ≥100 Schlägen/min).

*Interventionen:* Hochdosierte kontinuierliche Amiodaron Infusion entsprechend eines institutionellen Behandlungsprotokols.

*Messungen:* Hämodynamische Daten, Säure-Basen-Status, und Einzelorganfunktionen wurden vor, 12, 24 und 48 Stunden nach dem Beginn der Amiodaron Infusion bei allen Patienten erfasst. Die Amiodaron Infusion (mittlere Dosis 24 h: 1625 ± 528 mg; 48 h: 2708 ± 895 mg) führte in 54% der Studienpatienten nach 12 h, in 64% nach 24 h und in 75% nach 48 h zur Wiederherstellung eines Sinusrhythmus. Herzfrequenz, zentralvenöser Druck, und Milrinon-Bedarf reduzierten sich signifikant bei allen Patienten. Dies war begleitet von einem signifikanten Anstieg des Schlagvolumenindex und des mittleren arteriellen Blutdrucks. Serumkreatinin- und -bilirubinkonzentrationen stiegen bei allen Patienten signifikant an.

*Schlussfolgerung:* Innerhalb von 48 Stunden führte eine hochdosierte kontinuierliche Amiodaron Infusion bei 75% der chirurgischen Intensivpatienten mit neu aufgetretenen SVRS und moderatem bis schwerem Multiorgandysfunktionssyndrom zu einer Konversion in einen SR. Eine signifikante Verbesserung der kardiozirkulatorischen Funktion war bei Patienten, welche unter Amiodaron Therapie in einen Sinusrhythmus konvertierten, deutlicher, allerdings konnte eine solche ebenso unabhängig von der Herstellung eines Sinusrhythmus nachgewiesen werden. Neben eines möglicherweise durch Amiodaron mediierten Anstiegs der Serumkreatinin- und -bilirubinkonzentrationen, wurden während des Studienzeitraumes keine wesentlichen Medikamenten-assoziierten Nebenwirkungen beobachtet.

**Schlüsselwörter:** Amiodaron, Hoch Dosis, Tachy-Arrhythmien, Intensivpatienten, Hämodynamik.

**Summary.** *Background:* New-onset supraventricular tachyarrhythmias (SVTA) are a complication contributing significantly to morbidity and mortality in surgical intensive care unit (SICU) patients. Although only few data on efficiency can be found in the literature, class III antiarrhythmics have become popular in the treatment of SVTA in critically ill patients.

*Setting:* 12-bed general and surgical ICU in a university teaching hospital.

*Design:* Observational, retrospective study.

*Patients:* 131 SICU patients with SVTA (narrow-complex non-sinus tachyarrhythmias with heart rates ≥100 bpm).

*Intervention:* High-dosage amiodarone infusion according to an institutional protocol.

*Measurements:* Hemodynamic data, acid-base status, and single organ functions were obtained in all patients before amiodarone infusion and at 12, 24, and 48 hours afterwards. Patients were divided into responders and nonresponders. Amiodarone infusion (mean dosage 24h: 1625 ± 528 mg; 48h: 2708 ± 895 mg) restored sinus rhythm in 54% of study patients within 12 h, in 64% within 24 h, and in 75% within 48 h. Heart rate, central venous pressure, and milrinone requirements significantly decreased in all patients; this was accompanied by a signif-

* No author has a conflict of interest with regard to drugs discussed in this manuscript.

icant increase in stroke-volume index and mean arterial pressure. Serum concentrations of creatinine and bilirubin increased in all patients.

*Conclusion:* High-dosage continuous amiodarone infusion during a period of 48 hours resulted in restoration of SR in 75% of SICU patients with new-onset SVTA and moderate to severe multiple-organ dysfunction syndrome. A significant improvement in cardiocirculatory function was more pronounced in responders but could be demonstrated irrespective of restoration of sinus rhythm in all patients. Apart from a possibly amiodarone-mediated increase in concentrations of creatinine and bilirubin, no major drug-related adverse effects occurred during the observation period.

**Key words:** Amiodarone, high dosage, tachyarrhythmias, critically ill, hemodynamics.

## Introduction

New-onset supraventricular tachyarrhythmias (SVTA) are a feared complication in critically ill patients and significantly contribute to postsurgical morbidity and mortality [1, 2]. In a recent study, we reported a 15% incidence of new-onset tachyarrhythmias in patients treated in a surgical intensive care unit (SICU) [3]; 98% of those tachyarrhythmias were identified as SVTA. Patients who developed SVTA experienced a significantly longer length of stay in the SICU and higher mortality rate than patients without tachyarrhythmias after surgery [3, 4].

Although different recommendations for treatment of SVTA in critically ill patients have been suggested, no "gold standard" has yet been defined. The primary goals of therapy are rapid correction of ventricular rate and early conversion of SVTA into sinus rhythm (SR). Direct-current cardioversion has often been suggested as the first-line treatment in hemodynamic instability [5, 6]; unfortunately, in contrast to medical patients, this has not been proven to be a successful therapeutic option for treatment of SVTA in SICU patients [7]. Consequently, a pharmaceutical agent that can reliably restore hemodynamic stability in critically ill patients with SVTA would be of major importance.

Amiodarone, a class III antiarrhythmic agent, has gained widespread use in both short- and long-term management of tachyarrhythmias; several reports in medical patients demonstrated it to be highly effective for treatment of supraventricular as well as ventricular tachyarrhythmias [8–10]. There have been only 0a few studies, with small numbers of patients, on the effectiveness of amiodarone for treatment of SVTA in intensive care patients, in particular SICU patients, with associated multiple-organ dysfunction syndrome (MODS).

The present study retrospectively investigated the impact of high-dosage continuous amiodarone infusion on restoration of SR in 131 SICU patients with new-onset SVTA. Cardiovascular response and single organ functions were monitored for 48 hours after the start of amiodarone therapy to detect possible adverse side effects.

## Patients and methods

Over a three-year period, all medical records of a 12-bed SICU were reviewed for patients with new-onset SVTA who received a continuous infusion of amiodarone (Sedacorone®; Ebewe, Unterach, Austria) according to an institutional protocol. During that period, all patients with new-onset SVTA received amiodarone for treatment. SVTA were defined as narrow-complex non-sinus tachyarrhythmias with heart rates ≥ 100 bpm lasting for longer than 30 minutes. Patients with a prior history of tachyarrhythmias and/or pre-existing antiarrhythmic therapy were excluded from the analysis. Patients developing more than one episode of SVTA during their SICU stay were enrolled only at the first episode. Routine SVTA workup consisted of a 12-lead ECG, analysis of arterial blood gases and serum electrolytes, and measurements of serum creatine kinase MB. Follow-up ECG recordings were performed daily or, in the case of sudden change in cardiac rhythm, on the bedside monitor.

All patients received amiodarone according to a strict institutional protocol. Amiodarone was continuously infused via a central venous catheter; no bolus injections were given. Administration of amiodarone was started at a dosage of 90 mg/h for a maximum of 12 hours, followed by dose reduction to 40–60 mg/h for a maximum of 72 hours, and continuous infusion of 20 mg/h for another 5–7 days. In some patients, amiodarone was then continued orally with 200 mg 3 times per day. Where restoration of SR was faster, or heart rate decreased below 90 bpm, amiodarone was instantly reduced to 20 mg/h; where the heart rate dropped below 60 bpm, amiodarone infusion was stopped. No study patient received anticoagulation therapy for atrial tachyarrhythmias, only for routine thrombosis prophylaxis or where patients were on extracorporeal circuits.

The following data were collected from all patients: demographics, including age and body weight, pre-existence of cardiac disease, type of surgery, MODS score (Appendix), presence of systemic inflammatory-response syndrome or sepsis [11] at onset of SVTA, length of SICU stay, and SICU mortality. Laboratory monitoring at onset of SVTA included serum concentrations of potassium, calcium, magnesium and phosphate, as well as arterial oxygen partial pressure to rule out reversible causes of SVTA.

Hemodynamic data, including heart rate, mean arterial pressure, central venous pressure, mean pulmonary arterial pressure, cardiac and stroke-volume index, as well as norepinephrine and milrinone requirements were obtained before amiodarone infusion and at 12, 24, and 48 hours afterwards. Acid-base status and laboratory examinations to evaluate hepatic, renal and hematologic organ systems and creatine kinase MB isoenzyme concentrations were obtained at least once daily in all patients.

### *Statistical methods*

The primary aim of the study was to evaluate the rate of cardioversion into SR during amiodarone infusion. As a secondary aim, hemodynamic and single organ parameters were documented during the 48-hour observation period in order to investigate possible adverse side effects of amiodarone therapy. Patients were further grouped into responders and nonresponders to detect differences in hemodynamic and laboratory parameters at baseline and during amiodarone infusion. Responders were defined as patients converting into SR and maintaining SR during the observation period.

Demographic data were compared using Student's *t*-test, the $\chi^2$-test, or Mann-Whitney *U*-rank sum tests, as appropriate. Repeated measurements were analysed with a mixed-effects model (SAS PROC MIXED; SAS Institute, Cary, NC, USA) in order to account for death-related drop-outs [12]. If trends were

significant, comparisons with baseline were performed using the same model. Shapiro-Wilks tests were used to check for normality, which was approximately fulfilled in all reported variables except for aspartate aminotransferase, alanine aminotransferase, bilirubin, lactate, creatine kinase MB, and thrombocyte count, which were log-transformed. Because of the explorative character of the study, no corrections for multiple comparisons were used. *P*-values $< 0.05$ were considered to indicate statistical significance. Data are given as mean values ± SD if not indicated otherwise.

## Results

During the 3-year review period, 131 SICU patients with SVTA were treated with a continuous infusion of amiodarone. Although 93% suffered from new-onset atrial fibrillation, only 7% developed regular narrow-complex tachycardia. Demographic data, type of surgery, degree of MODS, length of SICU stay, incidence of systemic inflammatory-response syndrome or sepsis, and SICU mortality are shown in Table 1. There were no significant differences between responders and nonresponders in parameters relating to demographics or SICU stay. Nonresponders showed a non-significant trend towards higher SICU mortality ($p = 0.1$). There were no differences in the rate of cardioversion to SR between cardiac surgery patients (46/61; 75.4%) and non-cardiac surgery patients (52/70; 74.3%) ($p = 0.884$). There were no differences between the groups in the incidence of pre-existing cardiac diseases (coronary heart disease, congestive heart failure) or in serum concentrations of potassium, calcium, magnesium and phosphate, or in arterial acid-base status at onset of SVTA. None of the patients suffered from electrolyte abnormalities or hypoxia at the start of amiodarone therapy.

During amiodarone infusion, SR was restored in 54.2% of patients within the first 12 hours, in 64% within 24 hours and in 74.8% within 48 hours (Fig. 1).

Table 2 shows serial hemodynamic variables, norepinephrine and milrinone requirements, and cumulative amiodarone dosages in all patients, both responders and nonresponders. Heart rate fell significantly in all patients (–37%) during the observation period, but the decrease was more pronounced in responders than in nonresponders. All patients had a significant decrease in central venous pressure (–10%) and milrinone requirements (–16%), accompanied by a significant increase in mean arterial pressure (+6%) and stroke-volume index (+65%). There were no significant changes in mean pulmonary arterial pressure, cardiac index and norepinephrine requirements during amiodarone infusion. Nonresponders received significantly higher amiodarone dosages than responders.

Single-organ laboratory parameters and $PaO_2/FiO_2$-quotients of all patients, both responders and nonresponders, are shown in Table 3. Serum concentrations of creatinine and bilirubin increased significantly during amiodarone infusion. No changes occurred in other parameters during the 48-hour observation period. There was no difference in any parameter between responders and nonresponders. During the 48-hour observation period, no patient developed ARDS or died from the direct consequences of pulmonary failure during the subsequent ICU stay.

## Discussion

In this retrospective analysis, 74.8% of SICU patients converted into SR within 48 hours during high-dosage

**Table 1.** Characteristics of study patients, responders, and nonresponders

| | | All | R | NR |
|---|---|---|---|---|
| Patients (n) | | 131 | 98 | 33 |
| Age | (years) | 68 ± 12 | 68 ± 12 | 67 ± 14 |
| Male sex | n (%) | 82 (62.6) | 58 (59.2) | 24 (72.7) |
| Body weight | (kg) | 74 ± 16 | 76 ± 18 | 69 ± 14 |
| Surgery | n (%) | | | |
| | cardiac surgery | 61 | 46 | 15 |
| | general surgery | 53 | 41 | 12 |
| | vascular surgery | 7 | 5 | 2 |
| | trauma surgery | 5 | 2 | 3 |
| | orthopedic surgery | 5 | 4 | 1 |
| MODS | (points) | 7.5 ± 3.4 | 7.4 ± 3.4 | 7,9 ± 3.5 |
| SICU stay | (days) | 13 ± 10 | 13 ± 10 | 14 ± 11 |
| SIRS | (%) | 33.3 | 31.7 | 38.2 |
| Sepsis | (%) | 23.9 | 24 | 23.6 |
| SICU mortality | (%) | 28.2 | 24.5 | 39.4 |

*R* responders; *NR* nonresponders; *MODS* multiple organ dysfunction syndrome score; *SICU* surgical intensive care unit; *SIRS* systemic inflammatory response syndrome. There were no statistically significant differences between responders and nonresponders. Data is given as mean values ± SD, if not indicated otherwise.

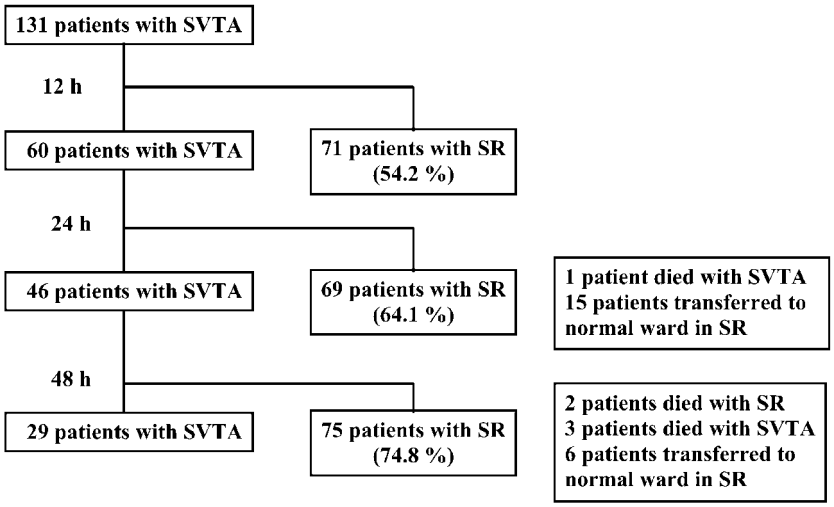


**Fig. 1.** Flow chart for the time course of therapeutic success of continuous amiodarone infusion during 48 hours in all study patients. *SVTA* supraventricular tachyarrhythmias; *SR* sinus rhythm

continuous amiodarone therapy. Fifty-four percent of patients converted into SR within 12 hours and 64.1% within 24 hours. During amiodarone infusion, all patients had a significant decrease in heart rate, central venous pressure and milrinone requirements, accompanied by a significant increase in mean arterial pressure and stroke-volume index. Although the drop in heart rate was less pronounced in nonresponders than in responders, both groups had significant improvement of global cardiocirculatory function.

Although no bolus injections had been used, the patients' cardioversion rate of 74.8% during the first 48 hours of amiodarone therapy corresponds with results of smaller studies in critically ill patients [13]. However, when compared with cardioversion rates during amiodarone treatment in perioperative and coronary care patients, the results of our study appear less good [8, 13–15]. The mean MODS score of the patients in our analysis was $7.5 \pm 3.4$ points, indicating that a substantial part of the study population suffered from moderate to severe MODS. In addition, most of the patients required norepinephrine and milrinone support because of cardiovascular instability. Disease severity and the extent of vasopressor and inotropic support have been identified as independent predictors for the development of SVTA in SICU patients [4]. Thus, a higher incidence and degree of multiple-organ dysfunction may explain lower cardioversion rates during amiodarone therapy in SICU patients compared with perioperative or coronary care unit patients receiving amiodarone therapy for new-onset SVTA [13].

The significant increase in stroke-volume index together with the simultaneous decrease in central venous pressure and milrinone requirements in all patients can be interpreted as substantial improvement of myocardial performance during amiodarone therapy. Several mechanisms could have contributed to this hemodynamic stabilization. Firstly, restoration of synchronised atrial contraction in patients with SVTA, in particular atrial fibrillation, could have increased ventricular end-diastolic volume and therefore significantly augmented stroke volume. The importance of this "atrial kick" for ventricular filling is even more pronounced in the typically elderly SICU patient and in critically ill patients with pre-existing left ventricular hypertrophy. Secondly, a significant amiodarone-induced decrease in heart rate prolonged diastolic time, which in turn improved myocardial blood flow and oxygen supply. Although this decrease in heart rate was less significant in patients without restoration of SR, it may have been sufficient to explain improvement of myocardial function in patients who did not respond to amiodarone therapy. Lastly, it could be hypothesized that amiodarone-mediated active coronary vasodilation [16] and direct positive inotropic effects [17] may have contributed to improved cardiac function during amiodarone therapy. On the basis of these hemodynamic results, it may be that control of heart rate rather than strict cardioversion in SR should be the primary therapeutic endpoint of antiarrhythmic therapy in critically ill patients with new-onset SVTA.

The observed amiodarone-induced stabilizing effects on cardiovascular function irrespective of restoration of SR are in contrast to some previous reports that described adverse hemodynamic effects during amiodarone therapy [18–20]. Most of these effects have been attributed to clinically relevant alpha- and beta-adrenoreceptor blockade associated with intravenous bolus injections of high-loading dosages [16, 21]. In contrast, the protocol used in our study patients avoided bolus injections and focused on continuous high-dosage infusion of amiodarone. Thus, even in critically ill patients, cardiocirculatory function was not impaired but seems to have been significantly improved by amiodarone infusion. Similarly, Kumar et al. reported a decrease in heart rate (–28%) accompanied by substantial improvement of stroke-volume index (+49%) and left ventricular stroke-work index (+61%) after slow i.v. amiodarone administration in patients with acute onset of atrial fibrillation or atrial flutter and severely depressed left-ventricular ejection fraction [14]; no adverse hemodynamic effects occurred during their study. Clemo et al.

**Table 2.** Serial hemodynamic parameters, norepinephrine, milrinone, and amiodarone dosages during continuous amiodarone infusion

| | | Baseline | 12 h | 24 h | 48 h | *p*-value |
|---|---|---|---|---|---|---|
| Patients (n) | | 131 | 131 | 115 | 103 | |
| HR | total | 137 ± 26 | 91 ± 17[b] | 91 ± 18[b] | 86 ± 16[b] | .0001[a] |
| (beats/min) | R | 139 ± 27 | 88 ± 15 | 87 ± 16 | 82 ± 14 | .0001[c] |
| | NR | 134 ± 21 | 99 ± 19 | 102 ± 20 | 98 ± 15 | |
| MAP | total | 78 ± 13 | 81 ± 13 | 80 ± 12 | 83 ± 12[b] | .004[a] |
| (mmHg) | R | 79 ± 13 | 82 ± 13 | 82 ± 13 | 83 ± 12 | |
| | NR | 77 ± 11 | 79 ± 12 | 76 ± 9 | 81 ± 12 | |
| MPAP | total | 27 ± 6 | 26 ± 6 | 25 ± 8 | 26 ± 6 | |
| (mmHg) | R | 26 ± 5 | 27 ± 7 | 26 ± 6 | 26 ± 5 | |
| | NR | 27 ± 7 | 26 ± 6 | 25 ± 10 | 26 ± 7 | |
| CVP | total | 10 ± 4 | 11 ± 10 | 9 ± 5 | 9 ± 4[b] | .0384[a] |
| (mmHg) | R | 10 ± 4 | 11 ± 11 | 9 ± 5 | 9 ± 4 | |
| | NR | 11 ± 3 | 11 ± 4 | 10 ± 4 | 9 ± 4 | |
| CI | total | 3.2 ± 1.1 | 3.2 ± 1 | 3.2 ± 0.9 | 3.3 ± 1 | |
| (l/min/m$^2$) | R | 3.2 ± 1.2 | 3.2 ± 1.2 | 3.2 ± 1 | 3.3 ± 1.1 | |
| | NR | 3.2 ± 1 | 3.3 ± 0.8 | 3.2 ± 0.8 | 3.3 ± 0.9 | |
| SVI | total | 23 ± 7.3 | 33 ± 10.5 | 33 ± 9.5 | 38 ± 5.5 | .0032[a] |
| (l/min/m$^2$) | R | 23 ± 6.8 | 36 ± 8.7 | 36 ± 7.9 | 40 ± 12.4 | |
| | NR | 24 ± 5.6 | 33 ± 7.8 | 31 ± 10.8 | 34 ± 9.8 | |
| NE | total | 0.46 ± 0.42 | 0.45 ± 0.33 | 0.43 ± 0.33 | 0.4 ± 0.38 | |
| (μg/kg/min) | R | 0.47 ± 0.4 | 0.46 ± 0.27 | 0.46 ± 0.31 | 0.4 ± 0.43 | |
| | NR | 0.45 ± 0.48 | 0.43 ± 0.43 | 0.37 ± 0.37 | 0.4 ± 0.29 | |
| MIL | total | 0.48 ± 0.16 | 0.49 ± 0.17 | 0.45 ± 0.16 | 0.4 ± 0.2[b] | .0008[a] |
| (μg/kg/min) | R | 0.47 ± 0.18 | 0.49 ± 0.2 | 0.46 ± 0.18 | 0.39 ± 0.25 | |
| | NR | 0.49 ± 0.11 | 0.5 ± 0.13 | 0.45 ± 0.13 | 0.4 ± 0.15 | |
| AMIO | total | | | 1625 ± 528 | 2708 ± 894 | |
| (mg) | R | | | 1579 ± 507 | 2586 ± 841 | .041[c] |
| | NR | | | 1760 ± 571 | 3045 ± 965 | |

*R* responders; *NR* nonresponders; *HR* heart rate; *MAP* mean arterial pressure; *MPAP* mean pulmonary arterial pressure; *CVP* central venous pressure; *CI* cardiac index; *SVI* stroke volume index; *NE* norepinephrine requirements; *MIL* milrinone requirements; *AMIO* amiodarone dosages; [a] significant time effect; [b] significant difference versus baseline; [c] significant difference between responders and nonresponders. Data is given as mean values ± SD.

[22] and Delle Karthe et al. [23] reported similar hemodynamic effects of heart-rate control during amiodarone infusion irrespective of cardioversion into SR. The results of those and our analyses strongly suggest that the hemodynamic effects of amiodarone significantly depend on the mode of administration, particularly in patients with cardiovascular instability, such as those who are critically ill.

A significant increase in serum concentrations of creatinine and bilirubin was observed during amiodarone therapy. To date, no adverse effects on renal function have been reported in association with high-dosage amiodarone infusion; however, Pollak et al. found significant elevation in serum concentrations of creatinine (11%) after one year of amiodarone treatment [24]. An increase in serum concentration of bilirubin during amiodarone therapy, as found in our patients, has not been reported before, although amiodarone has been associated with a two- to threefold increase in plasma concentrations of liver enzymes, in particular during initial treatment [25]. In most of our study patients, liver enzymes were already elevated before the start of amiodarone therapy and did not further increase during the observation period. Although possible amiodarone-mediated adverse effects on renal and hepatic function cannot be excluded during continuous high-dosage infusion, the observed increases in serum concentrations of creatinine and bilirubin may also be a consequence of evolving MODS and critical illness, since most of our study patients suffered from moderate to severe MODS.

One of the most serious non-cardiac side effects reported during amiodarone therapy is pulmonary toxicity; namely, pneumonitis and interstitial lung fibrosis in up to 15% of patients receiving long-term therapy [26, 27]. Concerns about acute pulmonary toxicity of amiodarone therapy in critically ill patients have been expressed recently [28]. During high dosage amiodarone therapy in our study patients, no change in the $PaO_2/FiO_2$-quotient was observed, suggesting clinically unchanged uptake of pulmonary oxygen during the observation period. However, the $PaO_2/FiO_2$-quotient may not be as sensitive as

bronchoalveolar lavage or lung diffusion capacity for carbon monoxide in detecting amiodarone-induced pulmonary toxicity [13]. Thus, although all toxicity cannot be reliably excluded, substantial impairment of pulmonary function seems to be unlikely during high-dosage amiodarone therapy in critically ill patients.

Some limitations in the results of this study need to be noted. The possibility that spontaneous cardioversion of SVTA into SR could have occurred in some patients without antiarrhythmic treatment is a drawback of most studies examining antiarrhythmic agents, including ours. However, critically ill patients with severe cardiovascular failure and depressed myocardial performance developing acute SVTA should not have control of heart rate and treatment aimed at immediate restoration of SR withheld. The present study therefore lacks a control group; in particular, the changes in laboratory parameters during amiodarone therapy can only be interpreted with caution. The design of this retrospective study also allows no insight into the time needed for control of heart rate associated with significant improvement in hemodynamic effects. On the other hand, the finding that 54% of the study patients cardioverted into SR after 12 hours of continuous amiodarone therapy and 75% after 48 hours suggests that amiodarone has rather slow antiarrhythmic actions when compared with other antiarrhythmic agents, e.g. class I.

In conclusion, high-dosage continuous amiodarone infusion during a 48-hour period resulted in restoration of SR in 75% of SICU patients with new-onset SVTA and moderate to severe MODS. Significant improvement in cardiocirculatory function was more pronounced in responders but could be demonstrated in all patients irrespective of restoration of SR. Apart from a possibly amiodarone-mediated increase in serum concentrations of creatinine and bilirubin, no major drug-related adverse effects occurred during the observation period.

**Table 3.** Laboratory parameters during continuous amiodarone infusion

| | | Baseline | 12 h | 24 h | 48 h | *p*-value |
|---|---|---|---|---|---|---|
| Patients (n) | | 131 | 131 | 115 | 103 | |
| $PaO_2/FiO_2$ | total | 251 ± 85 | 253 ± 87 | 243 ± 88 | 250 ± 78 | |
| | R | 247 ± 78 | 255 ± 84 | 245 ± 84 | 252 ± 73 | |
| | NR | 264 ± 101 | 248 ± 97 | 236 ± 99 | 246 ± 91 | |
| CK-MB | total | 21.8 ± 64.1 | 20.4 ± 53.3 | 16.7 ± 57.7 | 15.6 ± 34.8 | |
| (mg/dl) | R | 25.2 ± 73.3 | 23.7 ± 63.3 | 19.5 ± 67.5 | 15.9 ± 37.1 | |
| | NR | 11.1 ± 9.3 | 12.7 ± 11.6 | 9.4 ± 7.8 | 13.3 ± 15.2 | |
| Creatinine | total | 1.6 ± 0.9 | 2 ± 1.1[b] | 1.9 ± 1[b] | 1.9 ± 0.9[b] | .0056[a] |
| (mg/dl) | R | 1.6 ± 1 | 2.1 ± 1.1 | 1.8 ± 1 | 1.9 ± 0.9 | |
| | NR | 1.5 ± 0.5 | 1.8 ± 0.8 | 2.2 ± 1.1 | 2 ± 0.9 | |
| ASAT | total | 64 ± 241 | 93 ± 243 | 45 ± 107 | 94 ± 299 | |
| (U/ml) | R | 64 ± 261 | 95 ± 233 | 34 ± 59 | 100 ± 334 | |
| | NR | 61 ± 152 | 90 ± 270 | 77 ± 188 | 73 ± 124 | |
| ALAT | total | 62 ± 217 | 84 ± 230 | 30 ± 53 | 109 ± 324 | |
| (U/ml) | R | 66 ± 239 | 96 ± 256 | 23 ± 27 | 121 ± 364 | |
| | NR | 48 ± 106 | 54 ± 155 | 47 ± 93 | 69 ± 119 | |
| Bilirubin | total | 2 ± 2.2 | 2.6 ± 2.8 | 2.5 ± 2.7[b] | 3 ± 3.1[b] | .0385[a] |
| (mg/dl) | R | 1.9 ± 2.3 | 2.4 ± 2.8 | 1.9 ± 2.1 | 2.7 ± 3 | |
| | NR | 2.4 ± 1.4 | 3 ± 2.9 | 4.4 ± 3.2 | 4.2 ± 3.1 | |
| PT | total | 66 ± 15 | 64 ± 12 | 66 ± 13 | 67 ± 13 | |
| (%) | R | 68 ± 14 | 64 ± 12 | 68 ± 11 | 68 ± 14 | |
| | NR | 60 ± 16 | 62 ± 12 | 59 ± 15 | 62 ± 11 | |
| PTT | total | 43 ± 15 | 45 ± 12 | 42 ± 9 | 41 ± 8 | |
| (seconds) | R | 42 ± 15 | 44 ± 12 | 40 ± 7 | 40 ± 8 | |
| | NR | 47 ± 12 | 47 ± 10 | 47 ± 13 | 44 ± 8 | |
| Platelets | total | 148 ± 95 | 141 ± 82 | 145 ± 91 | 146 ± 102 | |
| (1000 cells/l) | R | 147 ± 96 | 148 ± 92 | 146 ± 97 | 155 ± 112 | |
| | NR | 51 ± 95 | 122 ± 43 | 143 ± 75 | 120 ± 62 | |
| Lactate | total | 18 ± 13 | 19 ± 15 | 19 ± 13 | 16 ± 9 | |
| (mg/dl) | R | 17 ± 13 | 18 ± 15 | 17 ± 12 | 15 ± 10 | |
| | NR | 21 ± 10 | 23 ± 16 | 23 ± 15 | 19 ± 7 | |

*R* responders; *NR* nonresponders; *CK-MB* creatine kinase MB; *ASAT* aspartate aminotransferase; *ALAT* alanin aminotransferase; *PT* prothrombin time; *PTT* partial thromboplastin time; [a] significant time effect; [b] significant difference versus baseline. Data is given as mean values ± SD.

**Appendix**. Definitions and grading of organ dysfunction (MODS-Score) (modified from Goris RJA et al. [29])

| Function | 0 | 1 | 2 |
|---|---|---|---|
| Pulmonary | $PaO_2/FiO_2 \geq 300$ | $PaO_2/FiO_2 \leq 250$ | $PaO_2/FiO_2 < 250$ |
| Renal | creatinine $\leq 2.0$ mg% | creatinine $> 2.0$ mg%; doubling of creatinine in patients with previous compensated renal failure | acute hemofiltration |
| Hepatic | bilirubin $< 2$ mg%; ASAT/ALAT within normal range | bilirubin 2–5 mg%; ASAT/ALAT $\leq 3$ times normal value | bilirubin $> 5$ mg%; ASAT/ALAT $> 3$ times normal value |
| Hematologic | thrombocytes within normal range; normal coagulation | thrombocyte decrease $\geq 25\%$; abnormal PT/aPTT with and without bleeding | hemorrhagic diathesis; massive transfusion 5 blood products/h or $> 10$ blood products/24 h |
| Cardiovascular | normal blood pressure; no vasoactive drugs except dopamine $\leq 5$ µg/kg/min | fluid resuscitation $> 50\%$ of normal need and/or dopamine $> 5\ \mu g \times kg^{-1} \times min^{-1}$, dobutamine $< 10\ \mu g \times kg^{-1} \times min^{-1}$, phenylephrine | dobutamine $> 10$ µg/kg/min, epinephrine, norepinephrine, combination of catecholamines, AVP, IABP, VAD |
| Gastrointestinal | normal gastrointestinal function, no bleeding | ileus $> 7$ days or bleeding requiring $\leq 6$ blood products/24 h | massive bleeding requiring $> 6$ blood products/24 h |
| Central nervous system | GCS $\geq 12$ | GCS 11–9 | GCS $\leq 8$ |

*$PaO_2$* arterial oxygen tension; *$FiO_2$* fractional inspiratory oxygen concentration; *ASAT* aspartate-aminotransferase; *ALAT* alanine-aminotransferase; *PT* prothrombin time; *aPTT* activated partial thromboplastin time; *AVP* arginine vasopressin; *IABP* intra-aortic balloon pump; *VAD* ventricular assist device; *GCS* Glasgow Coma Scale.

## Acknowledgements

This study was supported in part by the Lorenz Böhler Fond, Vienna, Austria.

## References

1. Artucio H, Pereira M (1990) Cardiac arrhythmias in critically ill patients: epidemiologic study. Crit Care Med 18: 1383–1388
2. Brathwaite D, Weissman C (1998) The new-onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. Chest 114: 462–468
3. Knotzer H, Mayr A, Ulmer H, Lederer W, Schobersberger W, Mutz N, et al (2000) Tachyarrhythmias in a surgical intensive care unit: a case-controlled epidemiologic study. Intensive Care Med 26: 908–914
4. Mayr A, Knotzer H, Pajk W, Luckner G, Ritsch N, Dünser M, et al (2001) Risk factors associated with new-onset tachyarrhythmias after cardiac surgery – a retrospective analysis. Acta Anaesthesiol Scand 45: 543–549
5. Nathanson MH, Gajraj NM (1998) The peri-operative management of atrial fibrillation. Anaesthesia 53: 665–676
6. Bender JS (1996) Supraventricular tachyarrhythmias in the surgical intensive care unit: an underrecognized event. Am Surg 62: 73–75
7. Mayr A, Ritsch N, Knotzer H, Dünser M, Schobersberger W, Ulmer H, et al (2003) Effectiveness of direct current cardioversion for treatment of supraventricular tachyarrhythmias, in particular atrial fibrillation, in surgical intensive care patients. Crit Care Med 31: 401–405
8. Vietti-Ramus G, Veglio F, Marchisio U, Burzio P, Latini R (1992) The efficacy and safety of short intravenous amiodarone in supraventricular tachyarrhythmias. Int J Cardiol 35: 77–85
9. Strasberg B, Arditti A, Sclarowski S, Lewin RF, Buimivici B, Agmon J (1985) Efficacy of intravenous amiodarone in the management of paroxysmal atrial fibrillation with fast ventricular response. Int J Cardiol 7: 47–55
10. Levine JH, Massumi A, Scheinmann MM, et al (1996) Intravenous amiodarone for recurrent sustained ventricular tachyarrhythmia. J Am Coll Cardiol 27: 67–75
11. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992) Definition for sepsis and organfailure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20: 864–874
12. Laird NM, Ware JH (1982) Random effects models for longitudinal data. Biometrics 38: 963–974
13. Hughes M, Binning A (2000) Intravenous amiodarone in intensive care. Time for a reappraisal. Intensive Care Med 26: 1730–1739
14. Kumar A (1996) Intravenous amiodarone for therapy of atrial fibrillation and flutter in critically ill patients with severely depressed left ventricular function. South Med J 89: 779–785
15. Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, et al (1995) Acute treatment of recent onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. Eur Heart J 16: 521–528
16. Podrid PJ (1995) Amiodarone: reevaluation of an old drug. Ann Intern Med 122: 689–700
17. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania Massie BM, et al (1995) Amiodarone in pa-

tients with congestive heart failure and asymptomatic ventricular arrhythmia. N Engl J Med 333: 77–82
18. Sugiyama A, Satoh J, Hashimoto K (2001) Acute electropharmacological effects of intravenously administered amiodarone assessed in the in vivo canine model. Jpn J Pharmacol 87: 74–82
19. Schwartz A, Shen E, Morady F, Gillespie K, Scheinman M, Chatterjee K (1983) Hemodynamic effects of intravenous amiodarone in patients with depressed left ventricular tachycardia. Am Heart J 106: 848–856
20. Shieh JP, Chu CC, Chen JY, Chen YH, Yeh FC, Hsing CH (1999) Acute fatal vasoplegia and asystole induced by intravenous amiodarone after cardiopulmonary bypass in a patient with preoperative cardiogenic shock. Acta Anaesthesiol Sin 37: 205–210
21. Venkatesh N, Padbury JF, Singh BN (1986) Effects of amiodarone and desethylamiodarone on rabbit myocardial beta-adrenoreceptors and serum thyroid hormones – absence of relationship to serum and myocardial drug concentrations. J Cardiovasc Pharmacol 8: 989–997
22. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA (1998) Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. Am J Cardiol 81: 594–598
23. Delle Karth G, Geppert A, Neunteufl T, Priglinger U, Haumer M, Gschwandtner M, et al (2001) Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias. Crit Care Med 29: 1149–1153
24. Pollak PT, Sharma AD, Carruthers SG (1993) Creatinine elevation in patients receiving amiodarone correlates with serum amiodarone concentration. Br J Clin Pharmacol 36: 125–127
25. Gill J, Heel RC, Fitton A (1992) Amiodarone – An overview of its pharmacological properties, and review of its therapeutic use in cardiac arrhythmias. Drugs 43: 69–110
26. Mason JW (1987) Drug therapy: amiodarone. N Engl J Med 316: 455–466
27. Rosenbaum MB, Chiale PA, Haedo A, Lazzari JO, Elizari MV (1983) Ten years of experience with amiodarone. Am Heart J 106: 957–964
28. Donaldson L, Grant IS, Naysmith MR, Thomas JSJ (1998) Acute amiodarone-induced lung toxicity. Intensive Care Med 24: 626–630
29. Goris RJA, te Boekhorst TPA, Nuytinck JKS, Gimbrere JSF (1985) Multiple-organ failure. Arch Surg 120: 1109–1115

Correspondence: Dr. Andreas J. Mayr, Division of General and Surgical Intensive Care Medicine, Department of Anesthesiology and Critical Care Medicine, Leopold-Franzens-University, Anichstrasse 35, A-6020 Innsbruck, Austria,
E-mail: andreas.j.mayr@uibk.ac.at

*(Received July 17, 2003, accepted after revision December 19, 2003)*