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Cardiac performance during vasopressin infusion in postcardiotomy shock

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Abstract *Objective:* Arginine-vasopressin (AVP) might be a potent vasopressor agent in catecholamine-resistant postcardiotomy shock. However, its use remains experimental because of considerations about deleterious effects on the heart. We report on the effects of continuous AVP-infusion on cardiac performance, biomarkers of myocardial ischemia, and systemic hemodynamics in catecholamine-resistant postcardiotomy shock. *Design:* Retrospective study. *Setting:* Twenty-one-bed general and surgical intensive care unit. *Patients:* Forty-one patients with catecholamine-resistant postcardiotomy shock. *Interventions:* Continuous infusion of AVP. *Measurements and results:* Heart rate (HR), heart rhythm, mean arterial pressure (MAP), central venous pressure, mean pulmonary arterial pressure, cardiac index (CI), stroke volume index (SVI), left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR) as well as milrinone and norepinephrine requirements were collected before and 1, 4, 12, 24, and 48 h after start of AVP infusion. Creatine kinase MB and troponin-I serum concentrations were measured daily. During AVP administration we observed a significant decrease in HR (–14.8%), milrinone (–17.5%), and norepinephrine requirements (–54.9%) as well as biomarkers of cardiac ischemia and a significant increase in LVSWI (+46.2%), MAP (+41.8%) and SVR (+60%). CI and SVI remained unchanged. Forty-five percent of postoperative new-onset tachyarrhythmias (TA) converted into sinus rhythm during AVP infusion. *Conclusions:* AVP was devoid of adverse effects on the heart in these patients with catecholamine-resistant postcardiotomy shock. The significant reduction in HR, vasopressor, and inotropic support suggest a substantial improvement in myocardial performance. These findings are supported by a significant decrease of cardiac enzymes and cardioversion of TA into sinus rhythm in 45.5% of patients with new-onset TA.

Keywords Arginine-vasopressin · Cardiac surgery · Shock · Heart · Vasopressor

Introduction

Cardiopulmonary bypass may lead to postcardiotomy shock, a syndrome characterized by vasodilatory shock sometimes accompanied by low cardiac index [1, 2]. Although the exact pathophysiology still remains obscure, excessive release of inflammatory mediators, inadequate surgery, and use of vasodilatory inotropes may be major contributing factors [3]. Mortality rates of postcardiotomy shock have been reported to exceed 70% [4].

Currently, catecholamines are the traditional vasopressor agents to support perfusion pressure in postcardiotomy shock. However, evolving catecholamine-resistance is a common clinical problem [5]. Adrenergic receptor

downregulation, acidosis, as well as excessive generation of nitric oxide and other vasodilatory mediators may all contribute to low catecholamine effectiveness [3, 6]. With increasing catecholamine dosages, however, several negative side effects on the cardiovascular system may occur. Tachyarrhythmias (TA), pulmonary hypertension with increased right ventricular afterload, increases of myocardial oxygen consumption, shortened myocardial relaxation time, and ß-adrenergic receptor downregulation can deteriorate cardiac performance. Ischemia, cardiomyocyte destruction, and myocardial infarction have been reported at very high catecholamine dosages [7].

In several studies and case reports low-dose infusion of arginine-vasopressin (AVP), a physiological hormone of the neurohypophysis, has been shown to be a potent vasopressor in postcardiotomy shock, in vasodilatory shock after left ventricular-assist device placement, as well as in other vasodilatory shock states [8, 9, 10, 11]. However, high dosages of AVP were reported to exert significant negative side effects on the heart. When used to control upper gastrointestinal bleeding high-dose AVP infusion led to myocardial ischemia and negative inotropic effects in up to 20% of patients [12]. In earlier reports ultra-high AVP dosages were even used as a stress test to provoke ischemic changes in ECG [13]. Therefore, intensivists hesitate to use AVP as an alternative vasopressor agent in catecholamine-resistant shock [14].

Between January 1998 and January 2001 forty-one patients with catecholamine-resistant postcardiotomy shock were treated with continuous AVP infusion in our institution. In this study we retrospectively analyzed the effects of continuous AVP infusion on cardiac performance, biomarkers of myocardial ischemia, and systemic hemodynamics.

Materials and methods

Between January 1998 and January 2001 all medical records of a 21-bed general and surgical intensive care unit (ICU) were reviewed for patients with catecholamine-resistant postcardiotomy shock who were treated with a continuous i.v. infusion of AVP (Pitressin®; Parke Davis, Berlin, Germany).

Catecholamine-resistant shock was defined as a failing effect of a stepwise increase of norepinephrine by 0.2 µg·kg·min over a 2-h period to keep mean arterial pressure (MAP) above 60 mmHg. All patients were volume-resuscitated according to the response of stroke volume index (SVI) to volume infusion. Normovolemia was assumed if a trial of further volume loading using colloids produced no effect on SVI. If SVI or cardiac index (CI) remained below 25 ml·beat·m² or 2 l·min·m² continuous milrinone infusion was started. AVP infusion was given continuously with dosages ranging from 4 U/h to 6 U/h. No bolus injections were used. After initiating AVP infusion norepinephrine therapy was targeted to maintain MAP equal to or above 60 mmHg in all patients. When MAP exceeded 60 mmHg norepinephrine infusion was stepwise decreased according to MAP. Norepinephrine was not completely withdrawn in any patient. AVP infusion was continuously reduced and tapered off when norepinephrine requirements fell below a dose of 0.3–0.4 µg·kg·min. In this situation weaning from AVP occurred first and individually according to the patients response to the stepwise decrease of AVP.

Table 1 Definitions and grading of organ dysfunction. (MODS Score; modified from Goris et al. [36]). (*PaO_2* arterial oxygen tension, *FiO_2* fractional inspiratory oxygen concentration, *ASAT* aspartate-aminotransferase, *ALAT* alanine-aminotransferase, *PT* prothrombin time, *aPTT* activated thromboplastin time, *AVP* arginine vasopressin, *IABP* intra-aortic balloon pump, *VAD* ventricular assist device, *GCS* Glasgow Coma Scale)

Function	0	1	2
Pulmonary	$PaO_2/FiO_2 \geq 300$	$PaO_2/FiO_2 \geq 250$	$PaO_2/FiO_2 < 250$
Renal	Creatinine ≤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 ≤ three times normal value	Bilirubin >5 mg%; ASAT/ALAT > three times normal value
Hematologic	Thrombocytes within normal range; normal coagulation	Thrombocyte decrease ≥25%; abnormal PT/aPTT with and without bleeding	Hemorrhagic diathesis; massive transfusion five blood products/h or > ten blood products/24 h
Cardiovascular	Normal blood pressure; no vasoactive drugs except dopamine ≤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, AVP, epinephrine, norepinephrine, combination of catecholamines, IABP, VAD
Gastrointestinal	Normal gastrointestinal function; no bleeding	Ileus >7 days or bleeding requiring ≤ six blood products/24 h	Massive bleeding requiring > six blood products/24 h
Central nervous system	GCS ≥12	GCS 11–9	GCS ≤8

The following data were collected from all patients: age, sex, admission diagnosis, preoperative ejection fraction, the Simplified Acute Physiologic Score (SAPS) [15], time on cardiopulmonary bypass, aortic cross clamp time, a MODS-Score (Table 1), ICU-mortality, and dosage and length of AVP infusion. In all patients creatine kinase MB (CKMB) and troponin-I (TROP) serum concentrations were obtained immediately after surgery and at least once daily during the ICU-stay. SAPS-Score was calculated from worst physiologic data during the first 24 h. MODS-Score was calculated from data obtained during 24 h before onset of AVP infusion.

Hemodynamic data including heart rate (HR), MAP, central venous pressure (CVP), mean pulmonary arterial pressure (MPAP) as well as milrinone and norepinephrine requirements were recorded before and 1, 4, 12, 24, and 48 h after start of continuous AVP infusion. Pulmonary artery catheter measurements including cardiac output (CO), CI, SVI, and pulmonary capillary wedge pressure (PCWP) were measured before and 1–3, 4–8, 12–16, 24±5, and 48±5 h after start of AVP infusion. Left ventricular stroke work index (LVSWI), right ventricular stroke work index (RVSWI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated according to standard hemodynamic formulas.

Postoperative new-onset TA defined as a non-sinus rhythm exceeding 100 bpm were recorded by continuous ECG-monitoring on the bedside screen and noted in the patients protocols. A 12-lead ECG was performed daily and in case of new-onset TA.

Statistical analysis

Exploratory methods were performed to describe demographic data. Repeated measurements were analyzed using a mixed effects model (SAS PROC MIXED, SAS Institute, Cary, USA) in order to account for death-related drop-outs [16]. Variables which did not meet normality assumptions (PVR, CKMB, TROP) were log-transformed. If trends were significant comparisons versus baseline were performed using the same model. Due to the explorative character of the study no corrections for multiple comparisons were used. *P*-values <0.05 were regarded as statistically significant. Data are given as mean values±standard deviations (SD).

Results

During the observation period 991 cardiac surgery patients were admitted to the intensive care unit. Forty-one patients (male, *n*=30; female, *n*=11) developed catecholamine-resistant postcardiotomy shock and severe MODS (MODS-Score 10.7±1.6 points) and received continuous AVP infusion (0.0012±0.0008 U·kg·min) for a mean period of 64±56 h. Demographic data of the study population are shown in Table 2. ICU-mortality in patients with postcardiotomy shock was 53.7%. In contrast, overall mortality from elective cardiac surgery was 2.8% and from emergency cardiac surgery 27% during the observation period.

Table 3 presents serial hemodynamic data as well as milrinone and norepinephrine requirements during continuous AVP infusion. AVP led to a significant decrease in HR. There were no significant changes in CI and SVI during continuous AVP infusion. LVSWI significantly increased. AVP caused a significant rise in MAP due to a significant increase in SVR. During the observation period milrinone and norepinephrine requirements significantly decreased by 17.5% and 54.9%, respectively. There were no changes in CVP, MPAP, PCWP, CO, RVSWI, and PVR during the observation period.

CKMB and TROP significantly fell in all patients with increased serum concentrations at study entry and remained low in patients without postoperative serum elevations.

Twenty-two patients experienced TA at study entry or during the observation period (atrial fibrillation 90.9%, regular, non-sinus rhythm tachycardia 9.1%). Ten patients (45.5%) converted into sinus rhythm during AVP infusion. One was started on antiarrhythmic medication simultaneously with AVP infusion. Six patients were already receiving a continuous infusion of amiodarone for at least 6 h before start of AVP infusion or did not receive any antiarrhythmic therapy (*n*=3). Three patients developed new-onset atrial fibrillation during AVP infusion.

Discussion

In this retrospective analysis continuous AVP infusion demonstrated no adverse effects on myocardial performance assessed by CI and SVI in catecholamine-resistant postcardiotomy shock. We observed a significant increase in LVSWI and MAP. This was accompanied by a pronounced decrease in HR. Simultaneously milrinone and norepinephrine requirements could be substantially reduced. In addition, 45.5% of postoperative new-onset TA converted into sinus rhythm during AVP infusion.

Despite the significant reduction in HR and inotropic support myocardial performance remained unchanged

Table 2 Characteristics of study population. Mean values±SD. (*ACBP* aorto-coronary bypass surgery, *surg* surgery, *Preop EF* preoperative ejection fraction, *CPB-Time* cardiopulmonary bypass time, *ACC-Time* aortic cross clamp time)

	All	ACBP	Valvular surg	Valvular surg+ACBP	Others
	41	26	8	3	4
Age (years)	71±8	73±5.5	65±12	74±4	66±6
Preop EF (%)	41±15	41±17	34	39±9	45
SAPS-Score	16±3.8	16±3.4	15±5	16±1.5	20±2.6
CPB-Time (min)	153±54	141±52	166±41	220±55	129±50
ACC-Time (min)	84±41	71±38	110±35	124±38	62
MODS-Score	10.7±1.6	10.7±1.6	10.8±1.8	11.3±1.2	10.3±1

Table 3 Cardiac parameters and systemic hemodynamics of study patients. Mean values±SD. [*HR* heart rate (beats/min), *CO* cardiac output (l/min), *CI* cardiac index (l/min/m^2), *SVI* stroke volume index (ml·beat·m^2), *LVSWI* left ventricular stroke work index (g-m·m^2·beat), *RVSWI* right ventricular stroke work index (g-m·m^2·beat), *MAP* mean arterial pressure (mmHg), *SVR* systemic vascular resistance (dyne·sec/cm^5), *CVP* central venous pressure (mmHg), *MPAP* mean pulmonary arterial pressure (mmHg), *PVR* pulmonary vascular resistance (dyne·sec/cm^5), *PCWP* pulmonary capillary wedge pressure (mmHg), *Milrinone* milrinone requirements (µg·kg·min), *Norepinephrine* norepinephrine requirements (µg·kg·min), *Troponin-I* troponin-I serum concentrations (mg/dl), *CKMB* creatine kinase MB (U/l)]

	0 h	1 h	4h	12 h	24 h	48 h	*P*-value
Number	41	41	38	36	32	21	
HR[a]	108±19	102±18	96±15[b]	94±16[b]	91±17[b]	92±16[b]	<0.0001
CO	6±2	5.4±1.5	5.7±2.1	5.5±1.5	5.5±1.4	5.3±1.4	0.3478
CI	3.3±1	2.9±0.8	3±1	3±0.9	3.1±0.9	2.8±0.8	0.0895
SVI	30±10	30±8	30±8	31±8	32±8	30±7	0.1578
MAP[a]	55±12	82±14[b]	78±12[b]	78±11[b]	76±12[b]	78±8[b]	<0.0001
MPAP	28±6	26±6	26±6	25±5	25±5	25±5	0.1255
CVP	12±4	13±4	12±3	13±2	12±3	12±3	0.8024
PCWP	16±4	16±4	15±4	15±4	15±3	16±5	0.5790
SVR[a]	733±305	1078±432[b]	1019±486[b]	1000±321[b]	1024±313[b]	1173±335[b]	<0.0001
PVR	168±108	1 64±68	168±85	159±81	188±86	162±65	0.3284
LVSWI[a]	17.3±8.3	25.7±8[b]	25±8.4[b]	26±7.9[b]	26.8±7.1[b]	25.3±6[b]	<0.0001
RVSWI	6±3.8	5.8±3.5	5.7±3	6.2±5.7	5.8±2.3	5.3±2.6	0.6455
Milrinone[a]	0.4±0.24	0.4±0.25	0.39±0.24	0.35±0.23	0.33±0.24[b]	0.33±0.23[b]	0.0205
Norepinephrine[a]	1.62±1.93	1.13±1.72	0.91±1.5[b]	0.58±0.94[b]	0.57±1.3[b]	0.73±1.63[b]	0.001
Troponin-I[a]	121±164				65±90[b]	43±53[b]	<0.0001
CK-MB[a]	37±64				28±41[b]	21±30[b]	0.0009

[a] Significant time effect
[b] Significant changes compared to baseline

during continuous infusion of AVP suggesting no deleterious effects of AVP on myocardial function. In contrast, our data indicate that AVP in the dosages used may even have positive inotropic effects on the heart. This is consistent with the work of Eyraud and Overand reporting improvement of myocardial performance during AVP infusion in catecholamine-resistant hypotension [17, 18].

Several mechanisms may account for the observed preservation of myocardial performance during AVP infusion. Increased MAP and thus increased coronary perfusion pressure leading to higher myocardial oxygen delivery could in part explain the observed improvement of myocardial performance.

High plasma norepinephrine levels have been shown to induce downregulation and uncoupling of myocardial beta-1 adrenergic receptors thus decreasing beta-1-mediated positive inotropic effects [1]. The significant decrease in norepinephrine requirements during AVP infusion may have causally reversed beta-1 receptor dysfunction thereby improving positive inotropic effects of norepinephrine on the heart.

Several in vitro and animal experiments suggest additional pharmacological mechanisms of AVP-mediated improvement in myocardial performance. First, numerous vasodilatory substances and mediators stimulate nitric oxide production in cardiac tissue exerting negative inotropic effects on the myocardium [19, 20]. AVP has been shown to attenuate endotoxin and interleukin-1beta-stimulated generation of nitric oxide thus possibly reversing negative inotropic effects of cardiodepressant mediators in postcardiotomy shock [21, 22]. Second, recent studies have shown that AVP increases intracellular calcium in myocardial cells through stimulation of V_1-receptors leading to a positive inotropic response [23, 24]. Third, AVP has been reported to enhance agonist-stimulated cAMP-formation in aortic smooth muscle cells by a calcium-calmodulin-dependent mechanism [25]. In cardiomyocytes this may amplify the positive inotropic action of norepinephrine and milrinone. Fourth, selective coronary vasodilatation and increased myocardial blood flow probably due to stimulation of V_1- and V_2-receptors have been demonstrated in animal experiments [26].

The significant reduction of elevated CKMB and TROP serum concentrations during the observation period further indicates absent deleterious effects of AVP on the myocardium when given as a continuous infusion at dosages not exceeding 6 U/h in catecholamine-resistant postcardiotomy shock.

These findings are in contrast to earlier reports indicating development of myocardial ischemia during bolus or continuous AVP infusion and negative inotropic side effects of AVP on the heart. Sirinek et al. reported a significant reduction in CO requiring isoproterenol infusion in awake patients with cirrhosis and portal hypertension when infusing AVP at a dosage of 40 U/h [27]. Shelly et al. found postmortem evidence of myocardial ischemia in 20% of patients with massive intraabdomi-

nal bleeding after infusion of AVP at dosages of up to 24 U/h [12].

Different dose regiments may attribute to controversial findings indicating dose-dependent effects of AVP on myocardial perfusion and performance. AVP dosages used in patients with upper gastrointestinal bleeding were 5–20fold higher than doses continuously given in catecholamine-resistant postcardiotomy shock [28, 29]. Furthermore, the negative inotropic effects of AVP commonly seen at very high dosages used to control upper gastrointestinal bleeding in normotensive subjects can be explained by strong baroreflex suppression of CO in response to massive AVP-mediated vasoconstriction. When used to achieve normotension in catecholamine-resistant postcardiotomy shock this baroreflex suppression of CO is absent.

The pharmacological mechanisms of AVP-mediated increases in arterial pressure are still a matter of speculation. However, four molecular pathways have been discussed. First, stimulation of vascular smooth muscle V_1-receptors by AVP increase cytoplasmatic ionized calcium via the phosphatidyl-inositol-bisphosphate cascade leading to arteriolar vasoconstriction [30]. Second, blockage of activated ATP-potassium channels within the smooth muscle cell membrane facilitates myocyte depolarization and thus vasoconstriction [31]. Third, under pathophysiologic conditions, AVP attenuates endotoxin and interleukin-1beta-stimulated generation of nitric oxide and its second messenger cyclic-guanosine-monophosphate thus inhibiting excessive arteriolar vasodilatation [21, 22]. Fourth, during endotoxinemia AVP has been shown to enhance adrenergic responsiveness through stimulation of smooth muscle V_1-receptors [32]. The last three mechanisms may be especially important in counteracting excessive vasodilatation in postcardiotomy shock.

An interesting finding of this study was the spontaneous cardioversion of TA into sinus rhythm in approximately half of patients with new-onset TA during AVP infusion. Although most patients already received a continuous infusion of amidodarone, the coincidence of cardioversion into sinus rhythm and simultaneous reduction in norepinephrine and milrinone requirements suggests a beneficial effect of AVP due to a reduction of catecholamine stress on the heart. High milrinone and catecholamine dosages are known to have substantial proarrhythmogenic effects [33, 34]. In a recent investigation we could demonstrate that severity of cardiovascular failure – which is mainly determined by the extent of catecholamine support to stabilize hemodynamics – is an independent predictor for the development of postoperative TA in cardiac surgery patients [35]. Therefore, it may be speculated that the significant reduction in norepinephrine and milrinone requirements together with an improvement of myocardial perfusion may have contributed to the observed high conversion rate of TA into sinus rhythm during continuous AVP infusion. Of course, restoration of sinus rhythm may have further been a major contributing factor regarding the improvement of myocardial performance in patients with TA.

AVP given as a continuous infusion not exceeding 6 U/h proved to be devoid of adverse effects on the heart in these patients with catecholamine-resistant postcardiotomy shock. The observation of a significant reduction in heart rate, vasopressor, and inotropic support even suggests a substantial improvement in myocardial performance. These findings are supported by the observation of a significant decrease of cardiac enzymes and the spontaneous cardioversion of TA into sinus rhythm in nearly half of patients with new-onset TA. Therefore, AVP may provide an important additional treatment option in patients receiving high vasopressor and inotropic support after cardiac surgery.

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