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Inotropic Therapy for Cardiac Low Output Syndrome: Comparison of Hemodynamic Effects of Dopamine/Dobutamine versus Dopamine/Dopexamine

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Abstract
Objective: To examine the effects of a therapy with dopexamine/dopamine in comparison with a regimen of dobutamine/dopamine on the outcome of patients with profound cardiogenic shock.
Material and Methods: Twenty patients presenting with an acute cardiogenic shock assisted with mechanical ventilation, beeing refractory to a therapy with dopamine alone were analyzed. After persistence of low cardiac output syndrome (cardiac index <2.5 l/min/m^2) was confirmed, patients were treated either with receiving dopexamine (2 μg/kg/min) (group 1) or dobutamine (6 μg/kg/min) (group 2) in combination with dopamine (6 μg/kg/min) for 24 hrs. Hemodynamic parameters, urin production and clinical outcome were measured at intervals throughout the study. The groups were similar with respect to demographics and risk factors and there were no significant differences in the supportive treatment and hemodynamics at baseline.
Results: The dopexamine treated patients had lower myocardial oxygen consumption (9310 ± 2243 mmHg O_2/sec vs. 10621 ± 2552 mmHg O_2/sec) and lower mean arterial pressure (66 ± 11 mmHg vs. 71 ± 10 mmHg) after the 24 hrs treatment interval, but no one of the changes reached statistical significance. No differences were found between the two groups for other variables and the overall clinical outcome.
Conclusion: The present study revealed that neither substance is superior in the treatment of cardiogenic shock, even if the effect on myocardial consumption and the reported beneficial effects on renal and splanchnic functions might favour the use of dopexamine under certain circumstances.

Key words: Cardiogenic shock, dopexamine, dopamine, dobutamine, low cardiac output syndrome

Introduction

Cardiogenic shock, predominantely after acute myocardial infarction, is mainly characterized by a left ventricular systolic dysfunction leading to inadequate organ and tissue perfusion. Despite the fact that extensive clinical trials with current pharmacologic therapies were able to show benefical effects on both hemodynamics and symptomatology [1-3] the prognosis of patients suffering by cardiogenic shock remains poor [4, 5]. One of the main goals in the therapy of cardiogenic shock remains the interruption of its vivious circle by optimizing preload and afterload, and by promoting or restoring coronary blood flow [6]. Therefore intravenous positive inotrope substances play an important role in the short-term management of these patients [3, 5, 7-10, 29, 30]. Dopamine, which is a ß2 and DA1 agonist is frequently used to treat these conditions, as at low doses it has inotropic and vasodilator properties [11]. Despite the fact that proposed benifical effects on renal function [11] are a matter of controversy [12] and that higher doses of dopamine due to its α-agonist property can cause vasoconstriction with adverse effects like organ hypoperfusion and a higher myocardial oxygen consumption, it is still frequently used [13]. Recent studies indicated that it can be useful to add β-agonists like dobutamine and dopexamine with vasodilatory properties (possibly in the splanchnic region) to improve the organ perfusion [14-16]. Furthermore the combined use of dobutamine, dopamine and the intraaortic ballon pump (IABP) with or without mechanical ventilation has been shown to slightly improve the survival of patients in cardiogenic shock [17, 18]. The purpose of this study was to compare the effects of dopexamine and dobutamine in patients with profound cardiogenic shock treated conventionally with dopamine and mechanical ventilation.

Methods

This retrospective analysis consists of 20 consecutive patients admitted to our hospital with the diagnosis of cardiogenic shock. Transthoracal echocardiography was performed in all patients at hospital admission. Cardiogenic shock was defined by both clinical and hemodynamic criteria (adopted from 28): systolic blood pressure < 90 mmHg, oliguria, low cardiac output with a cardiac index (CI) < 2.5 l/min/m^2 and an increased pulmonary capillary wedge pressure (PCWP) ≥ 15 mmHg in the absence of hypovolaemia. While none of the patients did suffer from an acute cardiac ischemia (neither typical ECG- changes nor cardiac

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enzyme elevation) in 15/20 patients (75%) a coronary heart disease (CHD) was documented and for 5/20 patients (25%) the diagnosis of dilated cardiomyopathy was known.

Time Course and Treatment Strategy

All patients received a BIPAP ventilation by a ventilator and a pulmonary artery catheter for the hemodynamic measurements and monitoring. Arterial pH, oxygen and carbon dioxid tension were serially measured by standard techniques. Myocardial oxygen consumption was measured by the systolic pressure-volume area method [19].

The 20 consecutive patients with cardiogenic shock were treated for a minimum of 24hrs with receiving: (group 1) dopamine (initial dose of 6 μg/kg/min) and dopexamine (fixed dose of 2 μg/kg/min) or (group 2) dopamine (initial dose of 6 μg/kg/min) dobutamine (fixed dose of 6 μg/kg/min) to achieve a CI >2.5 l/min. Central venous pressure and PWCP were used to assess the adequacy of cardiac filling. All patients presenting with an ischemic cardiomyopathy (15/20 pts, 75%) received in addition to medical treatment (as described above) a supportive treatment with an intraaortic balloon pump (IABP) excepting four patients due to inadequate peripheral vascular status.

Hemodynamic measurements were obtained at baseline, in intervalls of 1h and after 24hrs. After the hemodynamic stabilization of the patients they were weaned from ventilation by standard procedures and from IABP if this was applied.

Statistical Analysis

Comparisons of continous variables were performed by paired or unpaired t-test. A p value of less than 0.05 was considered as significant.

Results

The clinical characteristics of the study groups are summarized in Table 1. No significant difference for any of the listed variables was found between the two groups of patients at baseline.

For hemodynamic parameters no significant differences were found between the two groups regarding CI (cardiac index), PAP (pulmonary arterial pressure), PCWP (pulmonary capillary wedge pressure) and HR (heart rate) for the 24 hrs treatment intervall (for details and p values see Table 2). The CI increased in both groups from 2.3 ± 0.5 l/min/m² (group1) and 1.9 ± 0.5 l/min/m² (group 2) to 2.5 ± 0.8 l/min/m² (group1) and 2.7 ± 0.5 l/min/m² (group 2) after 24 hrs of combined therapy. The mean PAP and mean PCWP values were almost constant at a value of appoximately 30 mmHg and 20 mmHg respectively. The heart rate declined after an initial increase after the start of the combined treatment to the baseline value of 89 ± 19 bpm (group1) and 101 ± 20 bpm (group 2).

In addition for the MAP (mean arterial pressure) and the myocardial oxygen consumption no significant difference was obtained (for details and p values see Table 2). The myocardial oxygen consumption in patients treated with dobutamine and dopamine were trendless. Whereas, an insignificant tendency to minor myocardial oxygen consumption values was observed in the patients treated with dopexamine and dopamine (group 1). The occurrence of anuria or oliguria caused by cardiogenic shock showed no significant differences in both treatment groups. Renal failure with anuria was ascertained in 4 patients in group 1 and 3 patients in group 2 during the 24 hrs observation period. In these patients a continuous venovenous hemodiafiltration was implemented. Finally there was no difference in the overall prognosis since none of the patients died in the 24 hrs intervall of the combined treatment and there was no significant difference in the all cause mortality rate after one year (4/10 pts [40%] for group 1 and 3/10 pts [30%] for group 2; for details and p values see Table 1).

Discussion

The present analysis compared the effects of dopex-

Table 1. Baseline characteristics of study groups (mean ± SD).

Characteristics	Dopexamine (group 1, n = 10)	Dobutamine (group 2, n = 10)	p-value
Age, year	66 ± 6	62 ± 8	ns
Sex, M:F	7:3	6:4	ns
NYHA class IV, %	100	100	ns
Heart failure cause (n)			
Ischemic heart disease	7	8	ns
Dilated cardiomyopathy	3	2	ns
LV ejection fraction, %	20±3	22±6	ns
IABP (n)	5	6	ns
Death during 24 hrs intervall, %	0	0	ns
Death during one year, %	40	30	ns

Abbreviations: NYHA = New York Heart Association

Table 2. Hemodynamic parameters of study groups (mean ± SD). CI, PAP, PCWP, HR, MAP and Myocardial oxygen consumption values (mean ± SD) in the 24 hrs maintenance phase. For each time point the indicated values for the variables of group 1 and 2 are displayed in columns (indicated by 1 and 2 respectively above the column). (Abbreviations: CI cardiac index, PAP pulmonary arterial pressure, PCWP pulmonary capillary wedge pressure, HR heart rate, MAP mean arterial pressure and O_2cons Myocardial oxygen consumption).

Variable	Baseline		1 h		2h		4 h		8 h		12 h		16 h		24 h	
	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
CI ($l/min/m^2$)	2.3 ±0.5	1.9 ±0.5	2.8 ±0.6	2.5 ±0.4	2.8 ±0.8	2.7 ±0.4	2.7 ±0.6	2.5 ±0.4	2.6 ±0.6	2.9 ±0.5	2.7 ±0.7	2.7 ±0.7	2.6 ±0.5	2.7 ±0.6	2.5 ±0.8	2.7 ±0.5
p-value	0.11		0.12		0.79		0.53		0.36		0.67		0.6		0.63	
mean PAP (mmHg)	34.1 ±8.5	32.4 ±6.6	31.7 ±7.6	27.5 ±8.7	28.9 ±8.6	28.3 ±7.5	32.8 ±9.2	27.6 ±6.0	32.8 ±8.9	29.6 ±8.5	31.2 ±9.5	31.2 ±12.1	31.2 ±6.9	27.9 ±7.2	32.3 ±10.8	29.3 ±5.8
p-value	0.58		0.25		0.8		0.12		0.36		0.6		0.36		0.58	
mean PCWP (mmHg)	24.1 ±5.6	20.4 ±7.4	21.1 ±6.0	17.1 ±10.1	18.6 ±7.4	16.6 ±7.1	20.8 ±5.6	17.2 ±6.0	21 ±7.1	18.3 ±8.2	20 ±6.9	19.4 ±9.2	21.3 ±4.7	18.3 ±7.0	21.6 ±7.8	17.9 ±5.0
p-value	0.08		0.08		0.55		0.17		0.4		0.73		0.24		0.32	
HR (bpm)	89 ±19	101 ±20	94 ±18	102 ±21	90 ±18	100 ±18	96 ±22	102 ±16	97 ±21	101 ±21	99 ±19	99 ±15	95 ±17	97 ±15	91 ±16	94 ±16
p-value	0.17		0.31		0.19		0.36		0.55		0.78		0.91		0.74	
MAP (mmHg)	73 ±10	74 ±9	65 ±11	67 ±13	65 ±8	69 ±9	65 ±7	69 ±7	69 ±7	71 ±11	69 ±12	69 ±6	69 ±13	70 ±9	66 ±11	71 ±10
p-value	0.91		0.77		0.39		0.27		0.51		0.71		0.89		0.39	
O_2cons (mmHg O_2/sec)	9982 ±1754	10882 ±2069	9638 ±1705	10502 ±2503	9192 ±1549	10450 ±1677	9736 ±1922	11487 ±2042	10415 ±2063	11311 ±2560	10473 ±1763	11305 ±2440	9596 ±1456	11022 ±2400	9310 ±2243	10621 ±2552
p-value	0.53		0.24		0.12		0.17		0.37		0.5		0.14		0.28	

amine and dobutamine in patients presenting with an acute cardiogenic shock treated with dopamine and mechanical ventilation. We did not observe significant differences in the effects of both drugs on CI, PAP, and HR. Furthermore no difference was obtained for the overal prognosis of the treated patients, neither in-hospital nor 1-year mortaility showed significant difference.

The results of this study demonstrated that dopexamine is well tolerated as a 24 hrs infusion in patients with profound cardiogenic shock. Compared to the addition of dobutamine to the standard therapy of dopamine and mechanical ventilation, dopexamine did not show the disadvantageous increase in myocardial oxygen consumption, as well as no increase in the MAP could be observed. No other adverse side effects, e.g. dysarrhythmias, were observed during dopexamine was adminstered to the patients.

These data are in line with the reported effects of dopexamine and dobutamine on systemic hemodynamics for other disease pattern like septic shock [20], postcardiac surgery low cardiac outpout syndrome [21] and the outcome after major abdominal surgery [22].

Despite the minimal effects on the hemodynamics, dopexamine and dobutamine are reported to have lower adverse effects than dopamine. The incidence of severe cardiac dysarrhythmias is lower in dopexamine treated patients when compared to a treatment with dopamine [21] which can be attributed to the β1 adreneric effects of dopamine. Since dopexamine or dobutamine were used in combination with dopamine in the present study, differences to a treatment with dopamine alone could not be adressed. Nevertheless nearly no severe dysarrhythmia was observed in both treatment groups, which could be attributed to the need of lower doses of either catecholamine to achieve hemodynamic stabilization in the combination treatment strategies in this study compared to a putative single treatment regimen with dopamine alone.

Further important aspects of catecholamine therapy in critical ill patients are renal function and splanchnic perfusion in the course of the disease. Adressing renal function by measurement of urine production and laboratory parameters we were not able to ascertain a significant difference between both treatment groups. Since the protective effects of dopamine on renal function were recently contested [12] the addition of either dopexamine or dobutamine could have benefical effects [21]. In the present study we observed no difference in the incidence of renal dysfunction or the necessity for continuous venovenous hemodiafiltration between both groups.

Dopexamine is reported to support splanchnic perfusion and therefore it might have benefical effects in critical ill patients [23, 24]. Recent studies indicated that the gut protection mediated by dopexamine is not fully explained by its effects on whole-body hemodynamics and oxygen transport variables alone but can be attributed to its anti-inflammatory properties [25, 26]. In contrast, a recent study showed that there is no significant effect for dopexamine and dobutamine on the microcirculation [27] supporting the conclusion that further studies have to be conducted to elucidate the exact roles of dopexamine and dobutamine in splanchnic protection in critical ill patients [14]. In the present study we observed no severe impairment (i.e. ischemia) in splanchnic perfusion in both groups. Since both aspects – renal function and splanchnic perfusion – were not addressed in detail in the present study no direct conclusion could be drawn regarding the role of dopexamine or dobutamine. Nevertheless the overall statement that no significant effect between both groups were observed is in accordance with the conclusion of a recent study which compared systemic and regional effects of dobutamine and dopexamine in septic shock [20].

In conclusion, for patients presenting with cardiogenic shock, this study has shown that:

a) the combined medical therapy of either dopexamine or dobutamine to the standard therapy with dopamine together with supportive treatment (e.g. mechanical ventilation, IABP) leads to an increase in cardiac output after 24 hrs (not significant),
b) other relevant hemodynamic parameters (e.g. PWCP, HR, MAP) remained almost uneffected, and
c) dopexamine do not escalate the myocardial oxygen consumption and considerating the reported benefical effects on renal and splanchnic functions it therefore might be favorit in the treatment of certain patients.

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