Effects of sodium-nitroprusside and urapidil on gas exchange and ventilation-perfusion relationships in patients with congestive heart failure

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ABSTRACT: Vasodilators usually decrease arterial Po_2 in patients with congestive heart failure (CHF) because of alteration in ventilation-perfusion ($\dot{V}A/\dot{Q}$) relationships. The effects of sodium nitroprusside (SNP) and urapidil (U), a new selective α_1-receptor antagonist, were investigated in seven patients with CHF. The distribution of ventilation and perfusion was examined using the multiple gas elimination technique. The haemodynamic responses to SNP and U were similar, cardiac index increasing by 25% with SNP and by 31% with U. Despite a similar increase of mixed venous oxygen tension, the arterial Po_2 decreased from 11.3±0.8 to 9.6±0.6 kPa (p<0.01) with SNP but remained unchanged (11.0±0.9 vs 11.4±0.8 kPa, NS) with U. SNP and U both increased perfusion to lung units with $\dot{V}A/\dot{Q}$ ratios of 0.1 or less with no change in shunt fraction. The fractional perfusion to total low $\dot{V}A/\dot{Q}$ ratios (low $\dot{V}A/\dot{Q}$ + shunt) was higher with SNP than with U (14.1±2.6 vs 9.5±2.3%, p<0.01). The results suggest that gas exchange and $\dot{V}A/\dot{Q}$ relationships are altered less with U than with SNP in patients with CHF.
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Vasodilator therapy has proved to be useful in the treatment of congestive heart failure [1–3]. Although the effects of vasodilator therapy on left ventricular function and the peripheral circulation have been extensively investigated, few studies have examined the effects of vasodilators on the pulmonary circulation and gas exchange in congestive heart failure.

Sodium nitroprusside and agents with selective α_1-adrenergic antagonist properties demonstrate similar balanced vasodilator effects on the systemic arterial and venous beds [4], and may be considered as potent pulmonary vasodilators as well [5, 6]. The ability of sodium nitroprusside to induce pulmonary vasodilation and to impair the efficiency of arterial oxygenation has been reported by numerous experimental [7, 8] and clinical studies [5, 9, 10]. In patients with congestive heart failure [9] or respiratory failure [10], the infusion of sodium nitroprusside is associated with a decrease of arterial Po_2 resulting from alterations in ventilation-perfusion relationships. These effects have been ascribed to an increased pulmonary blood flow and/or inhibition of hypoxic pulmonary vasoconstriction [7–13].

Despite their ability to induce pulmonary vasodilation [6], selective α_1-receptor antagonists do not abolish the pulmonary arterial hypoxic pressure response [14, 15]. Reduction of pulmonary vascular resistance may not, therefore, be associated with substantial alterations in ventilation-perfusion relationships in the lung, and the efficiency of arterial oxygenation should be maintained as previously observed in patients with chronic pulmonary artery hypertension treated with urapidil [16, 17].

Urapidil is a new selective α_1-adrenoreceptor antagonist. Apart from its α_1-adrenoreceptor-blocking potency, which is somewhat less selective than that of prazosin, urapidil may also affect vascular tone through central mechanisms involving stimulation of serotonin 1A (5-HT$_{1A}$) receptors [18].

We examined the effects of urapidil and sodium nitroprusside on haemodynamics and gas exchange in seven patients with severe congestive heart failure. To determine whether these drugs could have a different effect on arterial Po_2 and ventilation-perfusion relationships, we used the multiple inert gas elimination technique to determine the distribution of ventilation and perfusion during baseline conditions and during infusion of both sodium nitroprusside and urapidil in the same group of patients.

Patients

Seven patients (five male, two female: mean age 49 yrs, range 42–67 yrs) with clinical and radiographic evidence of left ventricular failure were selected for this study (table 1). Six of these patients had dilated cardiomyopathy, as assessed by a left ventricular end diastolic diameter above 60 mm at bidimensional echocardiography with a percentage fractional shortening index less than 25%: two patients had chronic coronary artery disease with remote myocardial infarction, and four patients had primary cardiomyopathy. The seventh patient had chronic hypertensive cardiomyopathy. None of these patients had valvular heart disease or chronic pulmonary disease.

Table 1. – Characteristics of patients

Patient no.	Age	Sex	Diagnosis	NYHA class
1	58	F	CAD, MI	IV
2	64	M	ID	IV
3	65	M	ID	IV
4	42	M	AM	III
5	51	M	ID	IV
6	60	F	CHC	IV
7	67	M	CAD, MI	IV

NYHA: New York Heart Association functional class; CAD: chronic coronary artery disease; MI: remote myocardial infarction; CHC: chronic hypertensive cardiomyopathy; AM: acute myocarditis; ID: idiopathic cardiomyopathy.

Methods

On the day prior to the study, all diuretics and vasodilator drugs were withheld to ensure a steady state before the administration of the test drugs. Digitalis and antiarrhythmics were maintained. All patients had flow directed thermodilution pulmonary artery catheters (model 93A-431-7F, Edwards Laboratories, Santa Ana, CA) and radial artery catheters placed for continuous pressure recordings for at least 24 h. The patients breathed air or supplemental oxygen through a circuit consisting of a tightly fitting mask and an oxygen blender (Vespal PPC, CFPO Air Liquide, Le Plessis Robinson, France). The study protocol was approved by the local Ethical Committee and informed consent was obtained from each patient.

Measurements

The following measurements were obtained in each patient:
1) Tidal volume and minute ventilation using a calibrated spirometer (model SE 302, Ohmeda, Maurepas, France).
2) Po_2 of a gas sample from the inspiratory limb of the oxygen blender (ABL 30, Radiometer, Copenhagen).
3) Arterial and mixed venous pH, Po_2 and Pco_2 (ABL 30).
4) Total haemoglobin and haemoglobin oxygen saturation (So_2) by spectrophotometry (OSM 2 Hemoximeter, Radiometer, Copenhagen).

5) Systemic and pulmonary vascular pressures (Hewlett-Packard transducers, model 1290 A, Andover, MA). The pressure tracings were recorded on a Gould Multichannel recorder (Gould Instruments, Ballainvilliers, France).
6) Cardiac output was measured using a thermodilution cardiac output computer (Edwards, model 9520A, Santa Ana, CA), the values reported being the mean of five determinations.
7) Heart rate was measured from a continuously recorded electrocardiogram lead.

Derived variables were calculated according to standard formulae: cardiac index (CI) = cardiac output/body surface area ($l \cdot m^{-2}$); systemic vascular resistance (SVR) = Psa - Pra/CI ($U \cdot m^{-2}$); pulmonary vascular resistance (PVR) = Ppa - Ppaw/CI ($U \cdot m^{-2}$); stroke volume index (SVI) = CI/HR ($ml \cdot beat^{-1} \cdot m^{-2}$). Oxygen consumption ($\dot{V}o_2$) was calculated as the product of cardiac index and the difference between arterial and mixed venous oxygen content ($AVdo_2$). Systemic oxygen transport was obtained from the product of cardiac index and arterial oxygen content. Venous admixture (percentage of total blood flow) was calculated with the equation of Berggreen as capillary O_2 content minus arterial O_2 content/capillary O_2 content minus mixed venous O_2 content.

Continuous ventilation-perfusion ($\dot{V}A/\dot{Q}$) distributions were assessed using the multiple inert gas elimination technique of WAGNER et al. [19] as described previously [10, 20]. Briefly, 5% dextrose equilibrated with six inert gases (sulphur hexafluoride, ethane, cyclopropane, halothane, ether and acetone) was infused into a peripheral vein. Arterial and mixed venous blood samples as well as mixed expired gas samples which were obtained from a specially designed heated mixing box in order to avoid condensation of water vapour and loss of the most soluble gases were analysed for inert gas concentrations with a Packard 429 gas chromatograph (Packard Instrument Co., Downers Grove, Illinois). The coefficient of variation of the determination of SF6 in our laboratory was 1.3% and 1.8% for the other five gases. For each patient the blood solubility coefficients of the six gases were determined and the inert gas partial pressures retention-solubility and excretion-solubility curves were constructed. Continuous-ventilation perfusion distributions were then calculated together with the overall mean $\dot{V}A/\dot{Q}$ and standard error of mean of the ventilation and the perfusion distributions. A residual sum of squares less than 8 was required for each determination to ensure compatibility between the distributions and the measured inert gas data. A computer assisted analysis of the $\dot{V}A/\dot{Q}$ distributions allowed the determination of right-to-left shunt ($\dot{Q}s/\dot{Q}t$), i.e. $\dot{V}A/\dot{Q}$ <0.005, and low $\dot{V}A/\dot{Q}$ area perfusion, i.e. $\dot{V}A/\dot{Q}$ between 0.1 and 0.005.

Protocol

Four successive sets of measurements were obtained. Baseline values of haemodynamics and gas exchange were measured prior to drug infusion. SNP infusion was then

started, and the infusion rate was adjusted to achieve at least a 20% increase of the cardiac index (SNP infusion rates ranged from 1.5–3 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Data were collected after 60 min had elapsed in stable conditions. SNP was then discontinued and, after another 60 min period, a second control set of haemodynamic and gas exchange data was performed to ensure that the patient had returned to the values of the first control data acquisition and that no rebound effects had occurred [21]. Then urapidil was administered as intermittent *i.v.* boli until cardiac index rose by at least 20% (mean dosage used = 0.75 mg·/kg^{-1}). When stable conditions had been established, the fourth set of data was collected. The sequence of the drug administration was dictated by the longer half-life of urapidil compared to SNP, which did not allow a cross-over study design.

The methodological procedure for measuring the distribution of ventilation-perfusion ratios by the six inert gas elimination technique did not allow more than three determinations for each patient in our laboratory. The baseline value for inert gas elimination was, therefore, determined either before SNP infusion or before U administration in a randomized order.

Statistical analysis

All data are presented as mean±SEM. Statistical analysis for values obtained during drug infusion was performed by analysis of variance for repeated measures model followed by a multiple range test when the F value indicated significant differences among group means. A p value less than 0.05 was considered significant.

Results

Haemodynamic response

The haemodynamic findings recorded during the control phases prior to drug infusion did not differ significantly before urapidil (U), or nitroprusside (SNP). All patients were characterized by elevated cardiac filling pressures (Ppaw 3.6±0.2 kPa; Pra 1.2±0.2 kPa) and low stroke volume index (29±3 ml·beat^{-1}·m^{-2}). The mean heart rate was 90±7 beats·min^{-1} prior to SNP infusion and 88±8 beats·min^{-1} prior to U infusion.

SNP infusion was associated with decrease in mean Psa, from 12±1.2 to 10.3±0.8 kPa (p<0.001) and an increase in CI, from 2.62±0.20 to 3.35±0.28 l·min^{-1}·m^{-2} (p<0.001). Similarly, after administration of U Psa fell from 12.5±1.3 to 10.7±1.2 kPa (p<0.001) and CI increased from 2.5±0.3 to 3.25±0.2 l·min^{-1}·m^{-2} (p<0.001). SVR decreased to a similar magnitude with both drugs, from 31.5±4 to 22.5±2 U·m^{-2} with SNP (p<0.001), and from 34±3.5 to 24±2.5 U·m^{-2} with U (p<0.001). The mean heart rate was unchanged by SNP or U. SVI was elevated by SNP from 29±3 to 38±3.5 ml·beat^{-1}·m^{-2} (p<0.001) and by U from 29±2.5 to 35.5±2.5 ml·beat^{-1}·m^{-2} (p<0.001). The degree of elevation of SVI between SNP and U was not statistically different. Cardiac filling pressures declined

in each patient and to a similar magnitude with both drugs. Ppaw fell from 3.6±0.2 to 2.4±0.1 kPa (p<0.001) with SNP and from 3.8±0.2 to 2.6±0.1 kPa (p<0.001) with U. Pra decreased from 1.2±0.2 to 0.4±0.2 kPa with SNP (p<0.001) and from 1.3±0.2 to 0.6±0.2 kPa with U (p<0.001). A consistent decrease in Ppa and PVR was also observed in each patient in response to SNP and U. During SNP infusion, Ppa decreased from 5.2±0.3 to 3.6±0.3 kPa (p<0.001) and PVR from 4.7±1 to 3±1 U·m^{-2} (p<0.01); a similar response was noted with U, Ppa decreased from 5.4±0.4 to 4±0.3 kPa (p<0.001) and PVR from 5.5±1.5 to 3.2±1 U·m^{-2} (p<0.001). The haemodynamic responses to U and SNP did not differ significantly in this group of patients with various types of congestive heart failure.

Blood gases

As shown in tables 2 and 3, SNP infusion was associated with a decrease in Pao$_2$ in all but one patient in whom it increased from 11.1 to 14.4 kPa (patient no. 6). Mean arterial Po$_2$ decreased from 11.3±0.8 kPa to 9.6±0.6 kPa (p<0.01) during SNP infusion, while mixed venous oxygen tension (P$\bar{v}$o$_2$) increased from 4.1±0.2 to 4.6±0.2 kPa (p<0.01). Arterior-venous oxygen difference (AVdo$_2$) consequently decreased from 6.7±0.2 to 5±0.3% (p<0.001) while the oxygen consumption remained unchanged (164±12 *vs* 172±9 ml·min^{-1}·m^{-2}). After administration of U, arterial Po$_2$ decreased slightly in five patients and increased in two patients. The slight decrease in arterial Po$_2$ secondary to U infusion (11.0±0.9 *vs* 11.4±0.8 kPa, NS) did not reach statistical significance and the mean Pao$_2$ was therefore higher with U than with SNP (p<0.02). Mixed venous oxygen tension increased from 4±0.2 to 4.6±0.2 kPa (p<0.001) in response to U infusion and AVdo$_2$ decreased from 69±4 to 52±2 ml·l^{-1}(p<0.001). Oxygen consumption and minute ventilation did not vary, arterial Pco$_2$ and deadspace remained unchanged with both drugs. SNP and U differed from each other with respect to changes in Pao$_2$ while P$\bar{v}$o$_2$ and AVdo$_2$ were altered to a similar extent. Despite dissimilar effects of the two drugs on arterial Po$_2$, oxygen delivery increased to a similar extent with U, (from 381±45 to 487±39 ml·min^{-1}·m^{-2}, p<0.001) and with SNP, (from 398±39 to 469±39 ml·min^{-1}·m^{-2}, p<0.01).

Ventilation-perfusion distribution

Baseline distribution of ventilation ($\dot{V}$A) and perfusion ($\dot{Q}$) showed a bimodal distribution with a fraction of 2.1±0.7% of total blood flow perfusing lung units associated with a low ventilation-perfusion ratio ($\dot{V}$A/$\dot{Q}$ <0.1) (table 3). The mean shunt fraction was small in these patients (1.6±0.6%) but patients no. 4 and no. 6 had substantial shunt fractions of 4.5% and 3.2%, respectively. SNP infusion was associated with a slight and insignificant increase in shunt fraction, from 1.6±0.6 to 3.6±1.9% NS) and with an increased perfusion of lung units with a low ventilation-perfusion ratio (from 2.1±0.7

Table 2. – Effects of sodium nitroprusside and urapidil on gas exchange

	Sodium nitroprusside		Urapidil	
	C	D	C	D
Pao_2 kPa	11.3±0.8	9.6±0.6*	11.4±0.8	11.0±0.9
mmHg	(85±6)	(72±5*)	(86±6)	(83±7)
$P\bar{v}o_2$ kPa	4.1±0.2	4.6±0.2*	4.0±0.2	5.7±0.2**
mmHg	(31±1.5)	(34.5±1.5*)	(30±1.5	(35±1.5**)
$S\bar{v}o_2$ %	53.5±2	61±1.5*	52.5±2.5	61±2**
$AVdo_2$ ml·l^{-1}	67±2	50±3**	69±4	52±2**
$\dot{V}o_2$ ml·min^{-1}·m^{-2}	172±9	164±12	166±10	167±9
SOT ml·min^{-1}·m^{-2}	398±39	469±39*	381±45	487±39**

Values are mean±SEM. *: $p<0.01$; **: $p<0.001$ for comparison (ANOVA) between drug-infused (D) and control (C) studies. Pao_2 and $P\bar{v}o_2$: arterial and mixed venous oxygen tension, respectively; $S\bar{v}o_2$: mixed venous oxygen haemoglobin saturation; $AVDo_2$: arteriovenous oxygen difference; $\dot{V}o_2$: oxygen consumption; SOT: systemic oxygen transport.

Table 3. – Blood gases and ventilation-perfusion relationships

Patient		FIo_2	Pao_2		$P\bar{v}o_2$		$\dot{Q}va/\dot{Q}t$	Shunt	low $\dot{V}a/\dot{Q}$	Total low $\dot{V}a/\dot{Q}$
no.		%	kPa	mmHg	kPa	mmHg	%	%	%	%
1	C	0.21	12.6	(95.0)	3.4	(25.5)	5.8	0.9	2.6	3.5
	SNP		11.6	(87.5)	4.2	(32.0)	10.6	3.0	2.1	5.1
	U		12.2	(92.0)	4.4	(33.0)	8.1	0.5	6.1	6.6
2	C	0.21	8.4	(63.0)	4.2	(32.0)	21.0	0.2	1.0	1.2
	SNP		6.8	(51.0)	4.0	(30.0)	34.0	0.8	10.0	10.8
	U		7.7	(58.0)	4.5	(34.0)	28.0	0.0	7.9	7.9
3	C	0.31	12.1	(91.0)	3.7	(28.0)	11.4	0.9	2.3	3.2
	SNP		10.2	(77.0)	4.4	(33.0)	18.5	2.2	11.6	13.8
	U		12.2	(91.5)	4.1	(31.0)	13.0	0.1	7.0	7.1
4	C	0.30	14.4	(108.0)	5.1	(38.5)	13.2	4.5	0.0	4.5
	SNP		9.6	(72.0)	5.2	(39.0)	29.0	15.1	4.7	19.8
	U		12.1	(91.0)	5.6	(42.5)	17.0	9.1	4.6	13.7
5	C	0.21	12.8	(96.0)	4.0	(30.5)	9.2	0.7	0.0	0.7
	SNP		9.2	(69.0)	5.2	(39.0)	22.3	1.6	11.3	12.9
	U		11.2	(84.5)	5.3	(40.0)	18.9	1.0	3.5	4.5
6	C	0.35	11.1	(83.5)	3.4	(26.0)	12.9	3.2	3.6	6.8
	SNP		11.7	(88.0)	4.1	(31.0)	13.3	1.3	10.2	11.5
	U		14.4	(108.0)	4.0	(30.5)	9.9	1.0	5.0	6.0
7	C	0.25	8.9	(67.0)	4.4	(33.0)	22.0	1.2	5.2	6.4
	SNP		7.8	(59.0)	5.0	(38.0)	32.5	3.2	22.0	25.2
	U		7.4	(56.0)	4.5	(34.0)	35.0	1.5	20.0	21.5
x̄±SEM	C		11.4±0.8	(86±6)	4.0±0.2	(30.5±1.5)	13.6±2.2	1.6±0.6	2.1±0.7	3.7±0.8
	SNP		9.6±0.1	(72±5*)	4.6±0.2	(34.5±1.5*)	23.0±3.5**	3.6±1.9	10.2±2.3**	14.1±2.6*
	U		11.0±0.9	(83±7)	4.6±0.2	(35.0±1.5*)	18.5±3.7*	1.9±1.2	7.7±2.1*	9.5±2.3*

Values are mean±SEM (n=7); *: $p<0.05$; **: $p<0.001$; for comparison (ANOVA) between drug-infused (SNP, sodium nitroprusside; U, urapidil) and control (C) measurements. Measurements obtained during SNP or U differed from each other with respect to Pao_2 ($p<0.02$), perfusion in total low $\dot{V}a/\dot{Q}$ ($p<0.01$) and venous admixture ($p<0.05$). FIo_2: fractional inspired O_2 tension; Pao_2 and $P\bar{v}o_2$: arterial and mixed venous oxygen tension, respectively; shunt: fractional perfusion of lung units with ventilation-perfusion ratio equal to 0; low $\dot{V}a/\dot{Q}$: fractional perfusion of lung units with ventilation perfusion ratio of 0.1 or less; total low $\dot{V}a/\dot{Q}$: shunt + low $\dot{V}a/\dot{Q}$; $\dot{Q}va/\dot{Q}t$: venous admixture.

to 10.2±2.3%, p<0.001). Perfusion in total low ventilation-perfusion ratios therefore increased substantially, from 3.7±0.8 to 14.1±2.6% (p<0.001) during SNP infusion (table 3). A significant increased perfusion in lung units with a low ventilation perfusion ratio (from 2.1±0.7 to 7.7±2.1%, p<0.01) was also produced by urapidil administration with no significant increase in shunt fraction (1.9±1.2% vs 1.65±0.6%, NS). Perfusion in total low ventilation-perfusion ratios was therefore increased after urapidil infusion, (from 3.7±0.8 to 9.5±2.3%, p<0.05) but to a lesser value than with SNP (9.5±2.3 vs 14.1±2.6%, p<0.01). Venous admixture similarly increased with both U and SNP but to a lesser value with U than with SNP (18.5±3.7 vs 23.0±3.5%, p<0.05). A typical example of alteration in the distribution of ventilation-perfusion ratios induced by U and SNP is shown in figure 1.
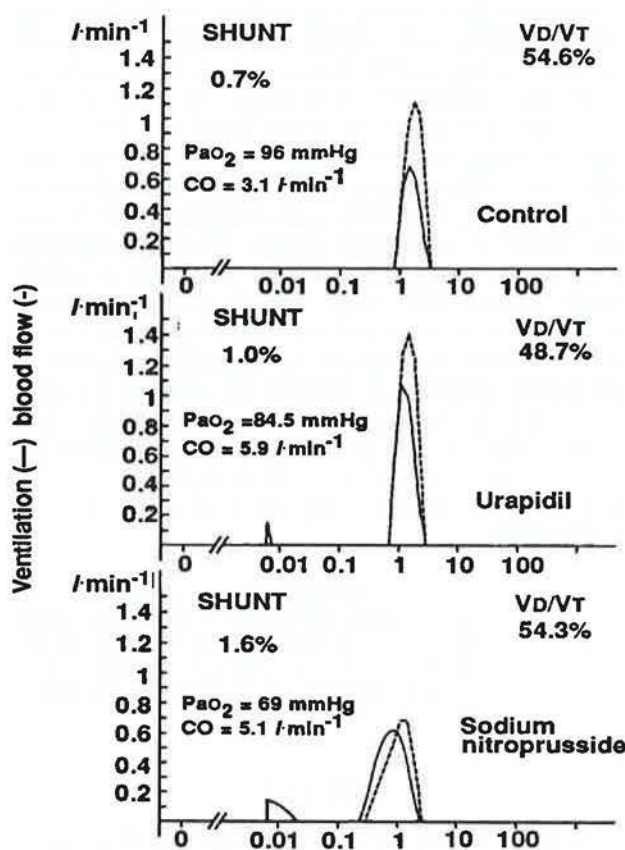

Fig. 1. – Distribution of ventilation-perfusion ratios under control conditions and after urapidil or sodium nitroprusside infusion in patient no. 5. CO: cardiac output; VD/VT: deadspace; Pao$_2$: arterial oxygen tension.

Discussion

The present study was designed to compare, in the same group of patients with congestive heart failure, the effects on pulmonary haemodynamics and gas exchange of SNP, a potent vasodilator with direct smooth muscle relaxant activity, and of urapidil, a new selective α_1-receptor antagonist, at doses achieving a comparable increase of pulmonary blood flow. SNP infusion caused a decrease in arterial Po$_2$ and marked alterations in ventilation-perfusion relationships. Urapidil and SNP infusion were associated with a similar decrease in Ppa and PVR, an equivalent increase in cardiac output, and thereby a similar increase in mixed venous oxygen tension. In contrast to SNP, the arterial Po$_2$ remained unchanged with urapidil because of lesser detrimental effects on ventilation-perfusion relationships.

Most vasodilators that have been used in the therapy of patients with congestive heart failure, chronic lung disease or respiratory failure have also been shown to affect arterial Po$_2$ [5, 9, 10, 22, 23] as a result of ventilation-perfusion mismatching due to redistribution of blood flow into the lung [9, 10, 23]. Increasing the cardiac output which increases mixed venous oxygen tension should theoretically improve arterial oxygen tension if shunt fraction is unchanged. However, human studies as well as laboratory investigations have largely supported the observation that shunt fraction increases with increase in pulmonary blood flow [24–27]. It is generally admitted that changes in mixed venous oxygen tension, by modulating the hypoxic pulmonary vasoconstriction, can largely contribute to this response [28, 29]. As cardiac output increases while oxygen consumption remains constant, Pv̄o$_2$ rises and varies directly with cardiac output; the ultimate effects of changes in Pv̄o$_2$ on Pao$_2$ will therefore be a function of both the increase in shunt and the rise in Pv̄o$_2$. An additional mechanism to explain why the efficiency of arterial oxygenation is impaired during vasodilator therapy may involve the direct negative influence of vasodilators on the pulmonary vascular tone in hypoxic lung units [11–13, 30].

In patients with congestive heart failure, the infusion of sodium nitroprusside has been reported to lower arterial Po$_2$ and to increase ventilation-perfusion mismatching [12]. In the present study, the multiple inert gas analysis similarly showed that SNP infusion was associated with an increased perfusion to functional lung units with ventilation perfusion ratios of 0.1 or less. The arterial Po$_2$ thus decreased concomitantly despite a significant increase of mixed venous oxygen tension. Redistribution of pulmonary blood flow to unventilated and poorly ventilated lung areas, therefore, probably occurred during SNP infusion as a consequence of the combined effects of increased cardiac output, increased Pv̄o$_2$ and inhibition of hypoxic pulmonary vasoconstriction. This latter mechanism, however, certainly played the most important role since alterations in ventilation-perfusion relationships can occur during SNP infusion in the absence of associated changes in cardiac output [10]. However, examination of individual values revealed that one patient increased his Pao$_2$ with SNP (patient no. 6, table 3). As compared to the others, patient no. 6 had one of the lowest Pv̄o$_2$ and increased his CI to 40% which was the highest increase induced by SNP in the group. This observation therefore would suggest that in some patients with low Pv̄o$_2$, increasing the CI should improve arterial Po$_2$ despite subsequent associated alterations in ventilation-perfusion relationships.

Urapidil administration produced cardiovascular effects similar to those of sodium nitroprusside; cardiac output improved and ventricular filling pressures decreased to a similar extent. These results are consistent with those obtained in a previous study comparing the systemic haemodynamic effects of sodium nitroprusside and of the selective α_1-receptor antagonist prazosin in patients with congestive heart failure [4]. Moreover, similar decreases in Ppa and PVR were measured in response to SNP or urapidil in our patients. Pulmonary vasodilation was difficult to assess in these patients with congestive heart failure since the decrease of Ppaw largely contributed to the reduction in Ppa, and since the decline in PVR was measured together with an increased cardiac output. Pulmonary haemodynamics, however, were altered to a similar extent with both drugs, providing a direct comparison of their respective effects on gas exchange. Arterial Po_2 remained unchanged with urapidil while fractional perfusion in lung units with low ventilation-perfusion ratios increased moderately but significantly. Perfusion to total low ventilation-perfusion ratios however increased less with urapidil than with SNP. The arterial Po_2 was therefore maintained with urapidil because of the associated increase in $P\bar{v}o_2$ but fell with SNP because of greater alteration in ventilation-perfusion relationships despite a similar increase of $P\bar{v}o_2$. This observation would suggest that the different ability of these agents to reduce the pulmonary vascular tone in hypoxic lung units accounted for their dissimilar effects on gas exchange.

Because the order of treatment was not randomized, we cannot exclude that the sequence order of the drug administration could possibly have influenced the results of this study. Since rebound haemodynamic events after abrupt withdrawal of nitroprusside have been described in patients with severe chronic heart failure [21], it is possible that activation of reflex vasoconstrictive forces during SNP therapy could have influenced the subsequent cardiovascular effects of urapidil administration. Such rebound changes however have been shown to be maximal within 10–30 min after SNP withdrawal with a quasi complete disappearance within one hour [21]. Such a phenomenum possibly occurred in our study since control measurements showed a tendancy for the systemic arterial, pulmonary arterial, and pulmonary arterial wedge pressures to be higher and for CI to be lower before urapidil than before SNP. If such mechanisms occurred, however, they should have attenuated rather than potentiated the effects of U. Moreover, this study was not conducted to compare the haemodynamic efficacy of the two drugs but only to qualitatively assess the gas exchange alterations induced by comparable changes in haemodynamics. It may be argued that discontinuation of diuretics and vasodilators 24 h prior to the beginning of the study did not warrant a steady state. Since only acute haemodynamic and gas exchange alterations were investigated in the present study, it can be assumed that suppression of vasodilation and diuretics had minimal influence on our results.

Hypoxic pulmonary vasoconstriction is not mediated or significantly affected by sympathetic nervous system activity; since α-adrenergic blockade does not abolish the pulmonary pressor response to hypoxia [14, 15], pulmonary vasodilation with selective α_1-receptor antagonist may occur without substantial alterations in gas exchange. In patients with chronic pulmonary artery hypertension and hypoxaemia we recently showed that urapidil could be used as a potent pulmonary vasodilator without altering gas exchange [16, 17]. The present results which extend these findings to patients with congestive heart failure are consistent with the beneficial pulmonary haemodynamic effects previously reported in such patients during selective α_1-receptor blockade with prazosin [6]. Although long-term therapy with urapidil in such diseases have not yet been studied, studies performed in patients with systemic hypertension have shown that tolerance to urapidil did not occur over one year [31].

Although the efficiency of arterial oxygenation was impaired during both urapidil and sodium nitroprusside infusion, cardiac output improved such that oxygen delivery was enhanced by both drugs. The mean increase of oxygen delivery for the whole group was not statistically different between urapidil and sodium nitroprusside. As cardiac output is the main determinant of oxygen delivery in patients with congestive heart failure, any benefit of vasodilator therapy on oxygen transport may thus be better appreciated on the degree of cardiac output improvement rather than on change in arterial oxygenation. In some patients with a small increase of cardiac output in response to vasodilator therapy, a substantial benefit may however be obtained by using drugs that do not greatly affect ventilation-perfusion relationships. The present results therefore indicate that selective α_1-receptor antagonists may be useful in patients with severe congestive heart failure and hypoxaemia.

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Effets du nitroprussiate de sodium et de l'urapidil sur les échanges gazeux et les relations ventilation-perfusion chez les patients en insuffisance cardiaque congestive. S. Adnot, P. Radermacher, P. Andrivet, J.L. Dubois-Rande, A. Dupeyrat, F. Lemaire.

RÉSUMÉ: Les vasodilatateurs provoquent habituellement une diminution de la Pao_2 chez les patients en insuffisance cardiaque congestive (CHF) en raison de l'altération des relations $\dot{V}A/Q$. Les effets du nitroprussiate de Na (SNP) et de l'urapidil (U), un nouvel antagoniste sélectif des récepteurs α_1, ont été étudiés chez 7 patients en CHF. La distribution de la ventilation et de la perfusion a été examinée par la technique d'élimination des gae multiples. Les réponses hémodynamiques à SNP et à U ont été similaires, l'index cardiaque augmentant de 25% après SNP et de 31% après U. Malgré une augmentation similaire de la tension d'O_2 de sang veineux mêlé, la Pao_2 a baissé de 11.3±0.8 à 9.6±0.6 kPa (p<0.01) après SNP, mais est restée inchangée après U (11.0±0.9 vs 11.4±0.8 kPa, NS). SNP et U ont tous deux augmenté la perfusion des unités pulmonaires dont le rapport $\dot{V}A/Q$ était de 0.1 ou moins, sans modifier la fraction shuntee. Les rapports de la perfusion fractionée sur les rapports $\dot{V}A/Q$ bas ($\dot{V}A/Q$ bas + shunt) sont plus élevés après SNP qu'après U (14.1±2.6 vs 9.5±2.3%, p<0.01). Ces résultats suggèrent que les échanges gazeux et les relations $\dot{V}A/Q$ sont moins modifiés après U qu'après SNP chez les patients en CHF.
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