Dopamine and the circulation in man

Citation for published version (APA):

Kho, T. L. (1987). *Dopamine and the circulation in man*. [Doctoral Thesis, Maastricht University]. Rijksuniversiteit Limburg. <https://doi.org/10.26481/dis.19870619tk>

Document status and date:

Published: 01/01/1987

DOI:

[10.26481/dis.19870619tk](https://doi.org/10.26481/dis.19870619tk)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Dopamine and
the circulation in man

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Proefschrift

ter verkrijging van de graad van doctor in de geneeskunde
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof. Dr. F.I.M. Bonke,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen op vrijdag 19 juni 1987
des namiddags om twee uur.

door

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*To Imelda and Marcia
In memory of my parents*

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Chapter 1: General introduction

Clinical studies on dopamine

Dopamine was long believed to be of functional significance only as a precursor of adrenaline and noradrenaline. It became a focus of primary interest only after the demonstration of its presence in relatively high concentration in various parts of the brain [1]. Thenceforward, studies on the effect of dopamine were done.

1.1 The cardiovascular system

In man, the hemodynamic effects of dopamine depend upon the dose administered. In normal subjects the intravenous infusion of dopamine ranging from 2 to 5 $\mu\text{g}/\text{kg}$ body weight/min, increases cardiac output [2] and renal blood flow [3, 4]. Heart rate does not change, and mean arterial blood pressure is either unchanged or slightly decreased. The increase in renal blood flow in normal subjects is usually accompanied by increments in glomerular filtration rate and sodium excretion [3]. With higher infusion rates of 5 to 10 $\mu\text{g}/\text{kg}/\text{min}$ i.v., arterial pressure, peripheral resistance and heart rate increase [5] and renal blood flow may decline. In animal studies, other mechanisms such as redistribution of intrarenal blood flow [6] and a direct action on the tubules have been considered to be responsible for the natriuresis [7].

Congestive heart failure was the first clinical indication for dopamine [8-10]. In patients with heart failure, the administration of dopamine with infusion rates of 2,1 to 5,8 $\mu\text{g}/\text{kg}/\text{min}$ increased cardiac index by 26% without a significant change in heart rate or total body oxygen consumption [9]. Peripheral resistance was reduced, and pulmonary resistance, when elevated, also fell. Glomerular filtration rate increased by 38%, renal blood flow by 79% and sodium excretion by an average of 48%.

Dopamine has also been found to be beneficial in patients with cardiogenic shock [11a, 11b], in patients with septic shock [12, 13] and in patients after cardiac surgery [14-17].

Subdivision of dopamine receptors into DA1 and DA2 receptors may explain the effect of dopamine in man. DA1 receptors are located postsynaptically. DA2 receptors are located presynaptically in the postganglionic sympathetic nerve terminals.

Stimulation of DA1 receptors causes smooth muscle relaxation, particularly in the renal, mesenteric, cerebral and coronary vascular beds, which in the cardiovascular system becomes manifest as vasodilatation. DA1 receptors are also located in other

vascular beds but appear to be reduced in number. Stimulation of DA2 receptors causes inhibition of the release of noradrenaline from postganglionic sympathetic nerve leads to a reduction in vascular tone and heart rate.

Dopamine also has beta-adrenergic effects. Stimulation of β_1 receptors causes an increment in cardiac contractility, cardiac output, heart rate and AV conduction. Stimulation of β_2 receptors causes vasodilatation primarily in the skeletal muscle and mesenteric vascular bed.

At higher doses, dopamine has also alpha-adrenergic effect.

Table 1 lists dopaminergic agonists, which act on one or more subtypes of receptors of the cardiovascular system.

Table 1:

Dopaminergic agonists, which act on the peripheral receptors of the cardiovascular system.

	DA1	DA2	β_1	β_2	α
Bromocriptine	—	+	—	—	—
Dopamine	+	+	+	—	+
Dopexamine	+	—	$\pm$	+	—
Fenoldopam	+	—	—	—	+
Ibopamine	+	+	+	+	+
Propylbutyl dopamine	$\pm$	+	—	—	+

1.2. The kidney

Dopamine infusion increases urine cyclic AMP excretion in man and this effect parallels the increased delivery of sodium into the renal tubule [18]. Both beta-adrenergic receptor stimulation and cyclic AMP have been shown to decrease proximal tubular reabsorption of sodium. It is possible that the natriuretic effect of dopamine is a combination of an action on beta-adrenergic receptors and also on a more specific renal vascular and tubular dopaminergic receptor. Dopamine infusions at rates that mostly activate DA1 and DA2 receptors only, may be useful in the treatment of acute renal failure [19-21], and in the pretreatment of unstable kidney donor [22]. These beneficial effects may be based on reversing the afferent glomerular arteriolar vasoconstriction thought to be important in the pathogenesis of acute renal failure [23, 24]. It should be noted that in some of these regimens dopamine has been combined with furosemide, and the latter compound has been shown to be capable of eliciting an increase in urine free dopamine [25]. In 21 patients with chronic renal insufficiency, with a mean creatinine clearance prior to therapy of 29 ml/min. oral administration of ibopamine, a dopamine analogue in a dose of 100 mg daily increased creatinine clearance by 31%. This remained unchanged after 6 months of administration [26]. Since gradual deterioration of renal function would be expected in these patients, the finding that ibopamine can improve renal function is of considerable clinical interest.

Dopamine excretion in human urine is 650-2285 nmol in 24 hours [27]. Initially the assumption was made that this reflected the filtered load of dopamine and was derived from the plasma, but it became apparent that urinary dopamine was much greater than could be accounted for by filtered plasma dopamine [28]. The administration of carbidopa, a peripheral dopa decarboxylase inhibitor, reduced the urine output of dopamine in man, at least temporarily, suggesting that a normal activity of renal dopa decarboxylase was necessary for renal production of dopamine [29]. Furthermore, after the oral administration of 250 mg of L-dopa to human volunteers, both plasma L-dopa and urine dopamine increased in similar proportion but plasma dopamine much less so [30]. Moreover, the kidney appeared to have sufficient decarboxylase activity to deal with increments in plasma L-dopa suggesting that conversion into dopamine was not rate-limited by enzyme but depended on the substrate concentration (L-dopa). It should be the uptake of L-dopa into the proximal tubule and other parts of the nephron which might be rate-limiting for conversion of L-dopa into dopamine.

Dopamine, 10.0 $\mu\text{g/kg/min}$, can release renin from the kidney in man [31]. However, lower doses of dopamine do not alter renin level [32-34]. It has been claimed that dopamine is an inhibitor of vasopressin release from the pituitary in man [35]. It is difficult to assess the relative importance of intrarenal interactions between dopamine, renin, vasopressin and other factors in man. Further studies will be required in order to assess their importance.

Factors that increase the output of dopamine in the urine are:

1. Changes in the electrolyte contents of the diet.

In normal subjects, who had a low salt diet (20 mmol sodium/day) for five days and a subsequently high salt diet (200 mmol sodium/day) for another five days, no significant alterations in plasma levels of dopamine and creatinine clearance were observed. During the first five days there was no significant change in urinary dopamine excretion. However, on the second day of the high salt diet there was a maximum increase in urinary dopamine excretion (from 1200 nmol/24 h to 1800 nmol/24 h) which gradually decreased in the following days, but was still significantly higher than the urinary dopamine excretion during the period of low salt diet. In contrast, the urinary sodium excretion reached the maximum on the third and following days during the high salt diet. This suggests that dopamine leads, rather than follows, sodium excretion. Moreover, the increase in urinary dopamine excretion, in the absence of changes in plasma dopamine after increased dietary sodium, implies that dopamine is formed within the kidney in response to sodium [36]. Further evidence for increased renal dopamine formation in response to a high salt intake is that kidney concentrations of dopamine rose in rats given a high sodium intake [37].

2. Administration of furosemide.

Furosemide, when given intravenously, increases the urinary output of dopamine significantly [25]. As furosemide inhibits active chloride transport in the ascending limb of the loop of Henle this can result in an increase in chloride concentration at the macula densa cells of the distal tubuli. The results of an animal study [37] show that the chloride ion seems to be an important determinant of renal dopamine production. Furosemide is known to be capable of increasing renal blood flow [38] and this may contribute to the diuretic effect. Both dopamine and prostaglandine production can be involved in this action on renal blood flow.

1.3 Essential hypertension

Detailed measurements have shown several hemodynamic abnormalities in essential hypertension [39]. Vascular resistance is increased several times more in the kidney as compared to other areas of the body. The filtration fraction is greatly increased in almost all patients who have essential hypertension. This suggests that the renal resistance is increased in both pre- and postglomerular renal vessels. By the time the patients develop severe essential hypertension, the renal blood flow is usually decreased to less than 60% of normal. It means that the kidneys of patients with essential hypertension require a very high renal arterial pressure to provide a normal urinary output. It is possible that the abnormal renal function results from some factor extrinsic to the kidney, which might include vasoconstrictor agents (noradrenaline, serotonin), agents that cause increased tubular reabsorption of electrolytes and water, or nervous stimulation of the renal vasculature. Thusfar, none of these factors has been proved to exist in the majority of essential hypertensive patients. This leads to the suspicion that essential hypertension is basically caused by intrinsic renal factors. One of them might be dopamine, which is an intrarenally generated natriuretic substance with renal vasodilatory effect. Failure, related to salt intake, in the production of dopamine, might be an important factor in the genesis of hypertension [40]. Further evidence that action on dopamine receptors can lower blood pressure in patients with essential hypertension has been reported [41, 42].

1.4 The adrenal gland

Aldosterone secretion in man may be under influence of dopamine [43, 44]. Administration of the dopaminergic receptor antagonist, metoclopramide, increases aldosterone secretion in normal man independent of known regulating factors [43, 45]. The observation that metoclopramide increases aldosterone secretion and that the dopaminergic receptor agonists dopamine and bromocriptine, do not decrease

basal aldosterone secretion in normal man have led to the hypothesis that aldosterone secretion is under maximum tonic dopaminergic inhibition [43, 44, 46]. If aldosterone secretion is modulated by a dopaminergic inhibitory mechanism, it is important to clarify the site of this mechanism. At present, the majority of evidence seems to indicate a direct adrenal cortical site of dopaminergic action, although a central nervous system mechanism also is possible. Since circulating quantities of dopamine are low [44] and far higher concentrations of circulating dopamine are required to inhibit metoclopramide-induced aldosterone secretion, it is unlikely that plasma dopamine contributes to aldosterone regulation.

Brown et al. in 1981 [47] have demonstrated stimulation of aldosterone secretion by metoclopramide in human adrenal adenoma cells in vitro. Although dopamine receptors have been identified in rat and calf adrenal zona glomerulosa cells in vitro [48, 49] evidence of the presence of receptors in human adrenal zona glomerulosa cells has not been reported. From the above mentioned findings, it is apparent that the weight of the evidence would favor a direct adrenal site of action of dopamine in the regulation of aldosterone secretion. Other evidence favouring this hypothesis includes the in vivo finding that metoclopramide seems to increase the immediate aldosterone precursor, 18-hydroxycorticosterone, in parallel with aldosterone in man [50]. So, a specific site of stimulation late in the aldosterone biosynthetic pathway would argue for a direct site of dopamine action. Additionally, since peripheral administration of dopamine blocks metoclopramide-induced aldosterone secretion, and since dopamine crosses the blood-brain barrier poorly, the current findings favour a peripheral site of action for dopamine in the adrenal cortex. Because of this many studies on the effect of dopamine were done.

In sodium-replete normal man, aldosterone responses, to gradual doses of angiotensin II infusions, were not altered by 4 $\mu\text{g/kg/min}$ of dopamine infusion [51]. This dose of dopamine resulted in approximately 70% attenuation of the aldosterone response to metoclopramide. In addition, this dose of dopamine failed to inhibit ACTH-induced aldosterone secretion. On the contrary, a quite different response is observed in sodium-deprived normal man, 4 $\mu\text{g/kg/min}$ of dopamine infusion significantly inhibited the aldosterone response to graded doses of angiotensin II infusion [52]. Moreover, enhanced aldosterone responses to metoclopramide in sodium depleted man have been observed [53]. Furthermore, a single oral dose (500 mg) of L-dopa, which did not affect plasma aldosterone concentrations in sodium-replete man, decreased basal plasma aldosterone concentrations in sodium-deprived man in balance at 10 meq/day sodium intake. Therefore, dopaminergic mechanisms appear to be more active in sodium-depleted than sodium-repleted man and seem to block angiotensin II steroidogenic action. In sodium-repleted state, the basal tonic dopaminergic inhibition of aldosterone and 18-OH-corticosterone in normal subjects and normal renin essential hypertensives [NREH] is comparable.

In patients with idiopathic hyperaldosteronism [IHA] and low renin essential hypertensives [LREH], an exaggerated response to the dopaminergic receptor antagonist,

metoclopramide, compared with the responses in normal subjects and NREH have been observed. This indicates that in these patients basal tonic dopaminergic inhibition of aldosterone secretion is elevated although less effective than in normal subjects and patients with NREH [54].

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Chapter 2: Dopamine and the heart

2.1 Introduction

Congestive heart failure is a growing public health problem both in terms of its magnitude and its poor prognosis. Since the prevalence of congestive heart failure increases with age, improvement in the average life expectancy would be expected to increase the magnitude of the problem. The mortality rate among patients with congestive heart failure is reported to be about 10% per year [1]. These mortality rates are even higher among patients who are unresponsive to the usual regimen of digitalis and diuretic drugs or who have more severe grades of congestive heart failure and approach 40 to 50% at 1 year [2].

Although it is suggested that congestive heart failure is not a disease, but a pathophysiologic state in which an abnormality of cardiac function is responsible for failure of the heart to pump at the rate required by the metabolizing tissues [3], abnormalities in cardiac output need not precede the observed increase in body salt and water retention [4, 5, 6]. A number of neurohumoral changes accompany congestive heart failure, which initially compensate the reduced flow but may overshoot and produce deleterious hemodynamic effects [7]. These changes include activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, as well as the release of arginine vasopressin [8, 9]. The ultimate results of these compensatory mechanisms is increased vascular tone, increased sodium and water retention and antidiuresis. Although it does seem likely that the sympathetic nervous system [10], the renin-angiotensin-aldosterone system [11], and the renal vascular response [12] participate in sodium retention in patients with advanced heart failure, the disturbances in sodium and water metabolism are not closely linked to any single variable but seem to be the result of the convergence of several determinants [13]. Furthermore, among patients with similar degrees of left ventricular dysfunction, there is a subset of patients with neurohumoral overactivation. This overactivation leads to severe impairment of sodium and water excretion, to renal dysfunction and to a less favourable clinical course. The results of the study of Mettauer et al. [13] suggest that the most important determinants for sodium excretion are activation of the renin-angiotensin-aldosterone system and ventricular function, and the most important for water excretion are plasma vasopressin, plasma noradrenaline and renal and ventricular function.

However, prostaglandins [14, 15] and atrial natriuretic peptide [16, 17] may also be important for sodium and water excretion.

Therapeutic possibilities

Digitalis glycosides

Digitalis glycosides, which inhibit membrane $\text{Na} + \text{K} + \text{ATPase}$ to increase intracellular calcium and, hence, increase contractile response and improve depressed ventricular function, are limited in terms of their modest potency and associated toxicity. The possibility that more than one inotropic mechanism of cardiac glycosides may exist has been discussed in detail by Noble [18] and is supported by ion-sensitive microelectrode studies carried out by Deitman and Ellis [19, 20]. However, studies of several populations of patients on maintenance digoxin treatment showed that the majority of those in normal sinus rhythm showed no deterioration in clinical status upon the withdrawal of the drug [21-26].

The controversial state of clinical efficacy of digitalis in patients with normal sinus rhythm has persisted despite a number of studies documenting positive inotropic effects in acute studies [27, 28]. Moreover, after 2 weeks of maintenance oral digoxin therapy, Carliner et al. [29] demonstrated an improved left ventricular performance in patients with compensated heart disease. O'Rourke et al [30] showed a decrease of left heart dimension in patients with cardiomegaly after myocardial infarction, and significantly improved shortening in both normal and abnormal segments at rest and during isometric exercise. Vogel et al. [31] observed that left ventricular ejection fraction had returned to control levels but were improved during isometric handgrip exercise. Furthermore, Arnold et al. [32] and Lee et al. [33] have demonstrated the beneficial hemodynamic effect and clinical improvement resulting from chronic maintenance digoxin administration in patients with chronic heart failure. Based on this evidence, one can reasonably conclude that conventional doses of digoxin do improve ventricular performance and also the clinical status of at least some, and probably the majority, of patients with symptomatic congestive heart failure [34].

Sympathomimetic and non-sympathomimetic positive inotropic agents

Although the sympathomimetic [35-41] and non-sympathomimetic [42-50], positive inotropic agents cause salutary short-term hemodynamic changes in resting patients with congestive heart failure, there are controversial long-term data [51-53] from controlled trials that indicate a persistence of the short-term hemodynamic improvement. Moreover, because of the moderate to high incidence of adverse side effects [49, 54-56] of some of these drugs, they have proved not to be clinically useful. Furthermore, positive inotropic stimulation has the potential to increase myocardial ischemia, particularly in the setting of coronary artery disease and intensification of ischemia could, in turn, cause myocardial necrosis, further worsening of ventricular function and cardiac arrhythmias [52]. Although several of these drugs have

been shown to reduce myocardial oxygen demand, presumably by causing a reduction in left ventricular wall tension [57-59], there is on a theoretical basis [52, 60, 61] a possibility of a detrimental effect on myocardial performance and consequently on patient survival of the long-term positive inotropic therapy. However, a progressive left ventricular dilatation after long-term administration of inotropic (Amrinone, Milrinone) or vasodilator (enalapril) agents has been observed. The fact that both types of agents produce the same end result despite fundamentally different modes of action suggests that stimulation of the heart from the inotropic agents is not in itself producing further damage [62].

Diuretics

In patients with mild to moderate congestive heart failure, despite the fall in renal blood flow as a result of a decrease in renal perfusion pressure and vasoconstriction of the renal arterioles, the glomerular filtration rate is usually normal, due to vasoconstriction of the efferent renal arterioles, which also lowers the hydrostatic pressure in the peritubular capillaries. The consequently increased filtration fraction causes an increase in colloid osmotic pressure in peritubular capillaries [63, 64]. Furthermore, renal blood flow is reduced preferentially in the outer renal cortex and a relative maintenance of perfusion in the juxtamedullary regions of the kidney in patients with congestive heart failure have been suggested [65], and this may also enhance net tubular sodium reabsorption. In this case, higher doses of furosemide reduce the sodium and water retention [13, 66]. In severe congestive heart failure there is an additional decrease in renal perfusion owing to a greater reduction in renal arterial pressure and more intense renal vasoconstriction, which involves both the efferent and the afferent renal arterioles. Hence, the glomerular filtration rate is reduced and the capacity of the kidneys to excrete sodium chloride and water is markedly decreased. Beside the reduction of glomerular filtration rate, secondary to an intrarenal feedback mechanism that couples distal salt delivery with filtration rate in individual nephrons, by diuretics [67, 68], furosemide increases plasma levels of noradrenaline and renin and systemic vascular resistance [69] leading to a decrease in renal perfusion and filtration rate. This may lead furosemide to be ineffective.

Vasodilators

The recognition that patients with congestive heart failure often have elevated peripheral vascular resistance which maintained adequate arterial pressure, but can simultaneously depress ventricular performance, has led to the introduction of vasodilator therapy. Vasodilators have emerged as an important component in the treatment of patients with heart failure and are particularly promising [70]. A wide spectrum of drugs is available: direct-acting vasodilators including sodium

nitroprusside [71-73], nitrates [74-76] and hydralazine [77-79], neurohumoral antagonist, prazosin [72, 73, 80, 81] and angiotensin converting enzyme inhibitors [82-86]. With most of these agents, short-term hemodynamic measurements show improvement, as do the clinical signs or symptoms of heart failure. However, for some drugs there have been contradictory reports of efficacy in the long-term. Whether this lack of efficacy during prolonged treatment is due to drug tolerance or to the natural and spontaneous deterioration of ventricular function is unresolved. The latter may partly be the cause of refractory congestive heart failure. The dismal survival rate of patients with severe heart failure is now well recognized [87] and has not been shown to be influenced by either vasodilator or inotropic therapy. Although in patients with moderate heart failure (mean maximal oxygen consumption 14.0-15.0 ml/kg/min, a level that would be consistent with NYHA class II or early class III congestive heart failure) hydralazine-isosorbide dinitrate therapy reduced borderline significantly [p is 0.05] the mortality rate within 3 years of follow up [88], in patients with class III congestive heart failure at the time of the study and the optimal medical management, nearly half of them died within the first year after initial study and by the end of two years a projected mortality of approximately 70 percent was calculated [89, 90]. It is clear that moderate-to-severe congestive heart failure is a very lethal disease and the present medical therapy, even if effective, leaves patients with an extremely poor prognosis. The ejection fraction, which reflects the extent of myocardial failure, correlates well with survival [91]. Whereas chronic converting enzyme inhibitor or inotropic therapy may improve blood distribution and thus result in symptomatic improvement, the underlying cardiac disease appear to progress and ultimately leads to the death of the patients [51, 92]. With these considerations in mind, in severe chronic heart failure, symptomatic relief is the primary goal of treatment. Dobutamine is a cardioselective sympathomimetic amine and can be derived from dopamine by modifying the side chain. It stimulates beta1-, beta2- and alpha-adrenergic receptors [93, 94], but it has no dopaminergic receptor-stimulating property [93]. Comparative cardiovascular effects of dobutamine and dopamine in patients with heart failure have been studied [95-97] and conflicting results of the chronotropic effects of both drugs have been reported. Acute effects of dopamine and dobutamine on hemodynamics, plasma levels of noradrenaline and renin in patients with low cardiac output after acute myocardial infarction are presented in 2.2. Chronic effects of dopamine on the excretion of salt and water excess and the renal function in patients with refractory congestive heart failure are reported in 2.3.

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2.2 Influence of dobutamine and dopamine on hemodynamics and plasma concentrations of noradrenaline and renin in patients with low cardiac output following acute myocardial infarction.

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Published in European Journal of Clinical Pharmacology, 1980, 18:213-217.

Summary

The comparative hemodynamic effects of dobutamine and dopamine were studied in 6 patients with low cardiac output resulting from acute myocardial infarction. Plasma levels of noradrenaline and renin were measured before and during a 5 $\mu\text{g/kg/min}$ infusion of each of the drugs. Dobutamine had a more pronounced chronotropic effect, increased the systolic arterial pressure more and decreased the systemic vascular resistance less than dopamine at doses which had comparable effects on cardiac output. Dobutamine stimulated renin release, which might partly be the cause of the increased systolic arterial pressure. The drug reduced the plasma level of noradrenaline, which might be explained as a reflex reduction in sympathetic tone. Dopamine, however, did not stimulate renin release but it did enhance the plasma level of noradrenaline, which might be due mainly to the release of endogenous noradrenaline.

Introduction:

Inotropic agents have been used for the treatment of heart failure in patients with low cardiac output. Many investigators have observed that isoproterenol improves myocardial performance [1-3], although the occurrence of adverse side-effects, such as tachycardia, ventricular arrhythmia and reduced perfusion pressure has often necessitated discontinuation of the drugs [4, 5]. Furthermore, isoproterenol has been shown experimentally to intensify myocardial ischemia, and to extend infarct size after coronary occlusion resulting in acute myocardial failure [6, 7].

It has been observed by some that dobutamine has less chronotropic and dysrhythmogenic effect than isoproterenol, when the effects on cardiac output are comparable; moreover, dobutamine has little effect on peripheral vessels [8-15].

In healthy subjects [16], and in patients with congestive heart failure [17, 18], intravenous infusion of dopamine in the restricted dose range (2-5 $\mu\text{g/kg/min}$) increased cardiac output without increasing heart rate or blood pressure. As dobutamine can be derived from dopamine by modifying the side-chain, some investigators have compared the hemodynamic effects of these two drugs. Few results of clinical studies are available and all the studies have been done in combination with cardiac glycosides and diuretics [19-21].

The aim of this study was to compare the inotropic and chronotropic effects of dobutamine and dopamine and their influence on noradrenaline and renin levels in untreated patients with low cardiac output caused by acute myocardial infarction.

Subjects and methods

Six untreated patients with low cardiac output (cardiac index 2.0 to 2.5 l/min/m² and pulmonary wedged pressure 14 to 16 mm Hg) following recent myocardial infarction and without arrhythmia, were studied. The mean age was 53 years (range 38-68 years); all subjects were male. The study was carried out three to seven days after the acute event. Informed consent was obtained prior to each study.

Electrodes were placed for recording and monitoring the electrocardiogram. After a catheter had been inserted into the brachial artery to record blood pressure, a triple-lumen thermodilution Swan-Ganz catheter was introduced percutaneously through a cubital vein and was placed in the pulmonary artery for measurement of cardiac output by the thermodilution technique [22], and for recording pulmonary wedged pressure.

After 30 min had elapsed, blood samples were collected for the determination of plasma noradrenaline [23] and renin [24]. Then arterial pressure and ECG were recorded and cardiac output was determined. Neither dopamine [22] nor dobutamine interfered with the determination of plasma noradrenaline concentration. The systemic vascular resistance index was calculated. Odd-numbered patients received dobutamine as the first drug and dopamine as the second drug, and even-numbered patients received dopamine as the first drug and dobutamine as the second drug. Both dopamine and dobutamine were administered by an infusion pump. The dose of each drug has increased in steps from 2.5 to 5.0 µg/kg/min at 20 min intervals. The same measurements were made when a new stable state of heart rate and blood pressure was achieved during each dose of infused drug. After the highest dose of the first drug had been infused, a wash-out period of 30 min followed. The hemodynamic parameters and plasma levels of noradrenaline and renin were determined again before the start of the second drug infusion, and in the stable state during each dose of the second drug infusion.

Statistical analysis utilized Student's paired t-test. A p value of less than 0.05 was considered to indicate a significant difference.

Results

Mean values of cardiac index, heart rate, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure and systemic vascular resistance index of the six patients before and during the infusion of the two doses of each drug are listed in table 1. A similar and significant enhancement of cardiac index during dobutamine and dopamine was observed. The percentage increments were 21.4 ± 6.0 and 31.0 ± 11.9 during dobutamine infusion and 21.7 ± 9.0 and 29.2 ± 12.2 during dopamine infusion, respectively. There was no significant difference in the enhancement of cardiac index during the dobutamine and dopamine infusions. A dose-related increase in

Table 1

Hemodynamic effects of dobutamine and six patients with low cardiac output resulting from acute myocardial infarction.

$\mu\text{g/kg/min}$	C	Dobutamine		Wash-out	C	Dopamine	
		2.5	5.0			2.5	5.0
C.I.							
mean	2.27	2.75	2.99		2.41	2.94	3.13
SEM	0.11	0.16	0.31		0.11	0.31	0.37
P	<0.05		<0.05			<0.05	<0.05
H.R.							
mean	73.7	77.2	84.5		79.8	82.2	80.2
SEM	4.8	5.5	4.5		4.4	4.4	5.0
P		n.s.	<0.05			n.s.	n.s.
S.A.P.							
mean	116.0	129.3	132.4		119.5	116.9	129.4
SEM	6.3	5.3	6.4		6.6	6.9	7.2
P		<0.05	<0.05			n.s.	n.s.
D.A.P.							
mean	64.2	66.5	66.7		67.0	63.2	64.6
SEM	4.1	3.4	3.6		4.4	3.4	3.8
P		n.s.	n.s.			n.s.	n.s.
M.A.P.							
mean	80.3	87.1	88.9		85.6	82.0	86.0
SEM	4.8	3.3	3.8		4.3	4.0	4.5
P		n.s.	n.s.			n.s.	n.s.
S.V.R.I.							
mean	2838.8	2572.0	2518.7		2855.3	2294.3	2282.3
SEM	144.4	160.1	290.0		153.6	143.9	178.7
P.		n.s.	n.s.			<0.01	<0.01

C	: Pretreatment or after wash-out period	
C.I.	: Cardiac Index	: l/min./m^2
H.R.	: Hearts Rate	: beats/min
S.A.P.	: Systolic Arterial Pressure	: mm Hg
D.A.P.	: Diastolic Arterial Pressure	: mm Hg
M.A.P.	: Mean Arterial Pressure	: mm Hg
S.V.R.I.	: Systemic Vascular Resistance Index	: $\text{dynes. sec. cm}^{-5}.\text{m}^2$

heart rate during dobutamine was obtained, with a significant elevation by $16 \pm 6.8\%$ during the infusion of $5.0 \mu\text{g/kg/min}$. During dopamine infusion, heart rate did not rise.

The systolic arterial pressure rose during infusion of both doses of dobutamine, by $12.4 \pm 5.7\%$ and $15.4 \pm 7.1\%$, respectively. Dopamine caused no statistically significant change in this parameter. No significant alteration of diastolic arterial pressure

was observed after either drug. During dopamine infusion, the diastolic arterial pressure tended to decrease, but the effect was not statistically significant. The differences between the changes during dobutamine and dopamine infusions were statistically significant (dobutamine versus dopamine: +2 versus -4 mm Hg, $p < 0.01$; and +3 versus -2 mm Hg, $p < 0.01$). The mean arterial pressure tended to increase during the dobutamine infusions, although no significant difference was observed. Dopamine did not alter the mean arterial pressure. However, substantial differences in the changes in mean arterial pressure during infusion of these two drugs were observed (dobutamine versus dopamine: +7 versus -4 mm Hg, $p < 0.01$) and +8 versus 0 mm Hg, $p < 0.02$). During both dobutamine infusions, systemic vascular resistance index decreased by $8.2 \pm 7.6\%$ and $10.3 \pm 11.0\%$, respectively, but neither difference was statistically significant (Table 1). A clear reduction in systemic vascular resistance index during the dopamine infusions was obtained, the decrements being $19.5 \pm 3.6\%$ and $19.9 \pm 5.5\%$, respectively.

Plasma renin concentration was significantly increased during the second dose of dobutamine (from 12.1 ± 3.1 ng AI/ml.h to 15.3 ± 3.6 ng AI/ml.h; an increment of 32%). In contrast, dopamine did not alter plasma renin concentration (from 13.4 ± 2.9 ng AI/ml.h to 13.5 ± 2.5 ng AI/ml.h; Fig. 1).

Fig. 1.
Influence of 5 µg/kg/min dobutamine and dopamine on plasma renin concentration (P.R.C.) in ng AI/ml · h. C: pretreatment and after wash-out period, respectively. *: $P < 0.05$.

Plasma noradrenaline concentration was significantly depressed during infusion of dobutamine 5.0 µg/kg/min (from 0.37 ± 0.07 to 0.28 ± 0.08 ng/ml; a decrement of 31.7%). However, there was a substantial elevation of plasma noradrenaline con-

centration during infusion of dopamine 5.0 $\mu\text{g/kg/min}$ (from 0.30 ± 0.05 ng/ml to 0.55 ± 0.09 ng/ml; an increment of 96%; Fig. 2).

P. Noradren. Conc.

Fig. 2.

*Influence of 5 $\mu\text{g/kg/min}$ dobutamine and dopamine on plasma noradrenaline concentration. C: pretreatment and after wash-out periode, *: $P < 0.05$.*

Discussion

Most investigators [19-21] have studied the comparative cardiovascular effects of dobutamine and dopamine in combination with cardiac glycosides and diuretics. Loeb et al. [19] found no difference in the chronotropic effect of these two drugs, while Stoner et al. [20] and Leier et al. [21] observed a greater increase in heart rate during dopamine infusion than during dobutamine infusion. On the contrary, Sakamoto and Yamada [14] and Kersting et al. [25] found a chronotropic effect during infusion of dobutamine 1.25-8.0 $\mu\text{g/kg/min}$ in patients who had not previously been treated with cardiac glycosides. This might be the explanation of the conflicting results, even if the cardiac glycoside was withdrawn 24 to 48 h before the study [26, 27]. In the present study, the increases in the cardiac index during dobutamine and dopamine infusion were comparable. At equieffective inotropic doses, it became apparent that dobutamine had a chronotropic effect. The absence of significant alteration in heart rate during dopamine infusion has previously been observed by Rosenblum et al. [17] and Beregovich et al. [18]. The increase in systolic arterial pressure during dobutamine infusion is comparable with the results of Gillespie et al. [28] and may partly be due to the increase in plasma renin. Intravenous administration of renin causes elevation of blood pressure [29].

The diastolic arterial pressure did not change significantly during either dobutamine or dopamine infusion. However, the difference between the changes was significant. The same results were found for the mean arterial pressure. This might have been due to the more pronounced decrease in systemic vascular resistance during dopamine infusion. The systemic vascular resistance index decreased during the infusion of dopamine and was not altered by dobutamine. The differences may in part be caused by stimulation of dopaminergic receptors [30].

The significant increase in plasma renin concentration during dobutamine infusion denotes that this drug acts strongly on beta-receptors of the juxta-glomerular apparatus, since renal blood flow does not change at all [30]. The substantial decrease in plasma noradrenaline level during dobutamine infusion may be explained as a reflex reduction in sympathetic tone. By contrast, the increase in plasma noradrenaline concentration during infusion of dopamine is mainly due to the release of endogenous noradrenaline, as has been shown by Nash et al. [31].

The results of the present study favour dopamine for the treatment of patients with low cardiac output following acute myocardial infarction, because both heart rate and arterial pressure are important determinants of myocardial oxygen consumption [32]. In addition, dobutamine increases regional myocardial perfusion much less in patients with coronary artery disease than in patients with normal coronary arteries [33]. In chronic and refractory low output cardiac failure, dobutamine in combination with cardiac glycosides and diuretics may be superior to dopamine, since severe heart failure is associated with a pronounced depletion of cardiac noradrenaline [34], and the inotropic effect of dopamine is in part mediated by release of stored myocardial catecholamines [13].

Acknowledgements

The authors wish to thank Dr. DeBruyne, Lilly, Brussels for supplies of dobutamine, Mr. Kret, Clin Midy, for supplies of dopamine (Intropin®). We are indebted to Ms. L. Baar, J. Moor and A.T. Erwich for their technical assistance, and to Miss G. Bost and Mrs. A. Lippinkhof for their help in preparing the manuscript.

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2.3 Combined therapy with high dose furosemide and low dose dopamine in refractory congestive heart failure

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Submitted for publication

Summary

The effect of high dose ($214 \pm 38,2$ mg) furosemide and combined therapy with high dose furosemide and low dose ($0,8 \mu\text{g/kg/min}$) dopamine on body weight reduction and serum creatinine were compared in 10 patients with refractory congestive heart failure.

During high dose furosemide the reduction in body weight was $0,42 \pm 0,10$ kg/day and the mean serum creatinine increased significantly from $134,1 \pm 17,0 \mu\text{mol/l}$ to $158,1 \pm 26,9 \mu\text{mol/l}$, whereas during the combined therapy the reduction in body weight was more than two-fold greater ($1,0 \pm 0,13$ kg/day) and the mean serum creatinine decreased significantly from $158,1 \pm 26,9 \mu\text{mol/l}$ to $128,1 \pm 19,3 \mu\text{mol/l}$.

Introduction

Some patients with pulmonary and peripheral edema due to congestive heart failure still remain symptomatic despite treatment with diuretics or vasodilators, inotropic agents, angiotensin converting enzyme inhibitors, bed rest and salt restriction [1-4]. Use of hemofiltration and ultrafiltration has been advocated as a method of managing refractory heart failure [5-8]. Loss of fluid, resulting in an important subjective and objective improvement of the clinical condition, has been achieved without deterioration of renal function. Moreover, patients become more responsive to standard heart failure therapy. Both techniques, however, are complex and expensive and less invasive methods of treatment for refractory heart failure are required.

It has been suggested that atrial natriuretic peptide might be useful in the treatment of refractory congestive heart failure [9, 10]. In this condition an excessive sodium and water retention and a marked reduction of renal plasma flow due to vasoconstriction are common findings. Atrial peptide might counteract these effects and is therefore theoretical of potential benefit. The results of a recent study, however, show no significant increase in either urine volume or sodium excretion by this peptide [11].

Dopamine, an endogenous precursor of norepinephrine is a sympathicomimetic amine, stimulates at low doses renal dopaminergic receptors. Thereby increasing renal cortical blood flow and promoting sodium excretion and diuresis [12, 13].

The aim of this investigation is to study the effect of low dose dopamine on body weight and renal function in patients with refractory congestive heart failure.

Patients and methods

Ten patients with refractory congestive heart failure, 8 women and 2 men, 55-85 years old were studied. Because of the precarious condition of the patients with refractory congestive heart failure, no cross-over randomized study could be done. The medical history and treatment of these patients are listed in table I. Six patients (case 2, 3, 4, 6, 7, 9) were taking 75 mg captopril daily, 2 patients (case 1, 5) 150 mg hydralazine and 60 mg isosorbide dinitrate daily and 2 patients (case 8, 10) 9 mg prazosin and 30 mg nifedipine daily, as vasodilator. All but one were on digoxin and all of them were taking furosemide 40-80 mg or bumetanide (1 mg) as diuretic.

Table I.

Medical history and treatment of patients with refractory congestive heart failure before the hospital admission.

	Sex	Age	Hypertensive Cardiomyopathy	Myocardial Infarction	Mitral in- sufficiency	Aneurysma cordis	Digi- talis	Diu- retic	Vasodilator
1	F	55	—	+	+	—	—	+	+
2	F	68	—	+	+	+	+	+	+
3	F	74	+	—	—	—	+	+	+
4	F	76	—	+	+	—	+	+	+
5	F	82	+	+	+	+	+	+	+
6	F	83	+	+	—	—	+	+	+
7	M	75	—	+	+	+	+	+	+
8	M	73	—	+	+	—	+	+	+
9	F	77	+	+	+	—	+	+	+
10	F	85	+	—	+	—	+	+	+

Abbreviations of table I:

F : female

M : male

age in years

+ : with

— : without

Table II lists the physical findings and serum creatinine concentration of these patients.

The study was performed in three consecutive periods.

In period I all drugs were continued and patients were put on bedrest, a diet of 2 gram sodium and a 1 liter fluid restriction. In period II higher doses (160-500 mg daily) furosemide i.v. were given whereas oral diuretics were stopped. The remaining drugs, diet and fluid restriction were continued.

In period III low dose (0.8 μ g/kg body weight/min) dopamine i.v. was added to the regimen, given in period II.

During these 3 periods body weight, blood pressure, heart rate and serum creatinine were regularly measured.

In 5 of the 10 patients, who were not incontinent of urine, creatinine clearances were measured before and during combined therapy with furosemide and dopamine.

Table II.

Physical findings and serum creatinine concentration of patients with refractory congestive heart failure on the day of hospital admission.

	BP		HR	Lung		Heart		Hepato- megaly	Ascites	Edema	Serum Creatinine μmol/l
	S	D		Rales	Effus	Gallop	Murmurs				
1	106	60	78	+	+	+	+	+	+	+	108
2	86	55	84	+	+	+	+	+	—	+	128
3	90	60	74	+	+	+	—	+	+	+	142
4	114	64	78	+	+	+	+	+	—	+	95
5	100	70	82	+	+	+	+	+	+	+	232
6	120	60	86	+	+	+	—	+	—	+	130
7	110	80	80	+	+	+	+	+	+	+	144
8	110	60	80	+	—	—	+	+	—	—	120
9	110	80	80	+	—	+	+	+	+	+	92
10	220	110	72	+	+	—	+	+	—	+	190

Abbreviations of table II:

BP : blood pressure mmHg
S : systolic
D : diastolic
HR : heart rate beats/min
Effus : effusion

Student's t-test for comparison of paired data was used. A p-value of less than 0,05 was considered to indicate a significant difference.

Results

Fig. I shows the body weight reductions, the alterations in blood pressure and heart rate, serum creatinine and creatinine clearance during high dose furosemide treatment (period II) and the combined therapy with high dose furosemide and 0.8 μg/kg body weight/min dopamine (period III).

The mean reduction in body weight during period II was $0,42 \pm 0,10$ kg/day. However, during period III body weight reduction was markedly enhanced ($1,0 \pm 0,13$ kg/day). The difference was statistically significant ($p < 0,005$).

Fig. 1.
The mean reduction in body weight, the mean alteration in blood pressure, heart rate, serum creatinine and creatinine clearance during the high dose furosemide treatment, and the combined therapy of high dose furosemide and low dose dopamine in patients with refractory congestive heart failure (n = 10).

Abbreviations of fig. 1.

BP : Blood pressure

Ccreat : Creatinine clearance

There were no significant alterations in blood pressure and heart rate during all three periods (Table III).

Table III.

Hemodynamic parameters in patients with refractory congestive heart failure before (period I) and after high dose furosemide (period II) and after a combination of high dose furosemide and low dose dopamine (period III).

	PERIOD I	PERIOD II	PERIOD III
S.A.P.			
MEAN	116.5	113.0	109.5
± S.E.M.	10.8	8.4	8.1
P		n.s.	n.s.
D.A.P.			
MEAN	71.9	72.0	68.0
± S.E.M.	5.2	2.6	4.1
P		n.s.	n.s.
H.R.			
MEAN	75.8	77.8	74.9
± S.E.M.	3.1	3.0	3.5
P		n.s.	n.s.
n	10	10	10

S.A.P. : SYSTOLIC ARTERIAL PRESSURE : mmHg
D.A.P. : DIASTOLIC ARTERIAL PRESSURE : mmHg
H.R. : HEART RATE : beats/min

The mean serum creatinine increased significantly from $134,1 \pm 17,0 \mu\text{mol/l}$ to $158,1 \pm 26,9 \mu\text{mol/l}$ ($p = 0,05$) during period II and decreased significantly from $158,1 \pm 26,9 \mu\text{mol/l}$ to $128,1 \pm 19,3 \mu\text{mol/l}$ ($p < 0,005$) when dopamine was added (period III).

The mean creatinine clearance of 5 patients who were not incontinent of urine, rose significantly from $24,0 \pm 5,6 \text{ ml/min}$ to $39,4 \pm 9,1 \text{ ml/min}$ ($p < 0,005$) during the combined therapy (fig 1).

In case 3 the alterations in serum creatinine and the reductions in body weight before and during the addition of low dose ($0,8 \mu\text{g/kg/min}$) dopamine to the high dose (250 mg daily) furosemide treatment were observed in two consecutive periods (fig. 2).

Serum creatinine rose markedly during the high dose furosemide treatment and decreased to below pretreatment value during the combined therapy of high dose furosemide and low dose dopamine. Serum creatinine rose evidently after the withdrawal of dopamine and decreased again after the administration of this drug was repeated.

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The reduction in body weight was more pronounced during the combined therapy than that during high dose furosemide treatment. The reduction in body weight disappeared after dopamine had been withdrawn and appeared again after the second administration of this drug.

Discussion

In mild and moderate congestive heart failure, 80-160 mg furosemide improves symptom-limited exercise tolerance and reduces fluid retention [14, 15]. In patients with severe congestive heart failure, higher doses of oral or intravenous dose of furosemide may be given. In this situation the therapeutic effect may also be the result of some reversal of the shunting of blood from cortical to juxtamedullary nephrons as commonly occurs in severe heart failure [16]. However, during the intravenous administration of $214 \pm 38,2$ mg furosemide daily to our patients with refractory congestive heart failure, we observed a significant increase in serum creatinine whereas fluid retention still existed. A further activation of renin-angiotensin system by high-doses furosemide in these patients, leading to an increase in renal vascular resistance may explain the deterioration of their renal function. It has been reported, however, that glomerular filtration rate can be reduced by an intrarenal feedback mechanism that couples distal salt delivery with filtration rate in individual nephrons [17, 18]. Moreover, an increment in peripheral venous compliance and a reduction of venous return can occur and lead to a decrease in renal function [19]. As blood pressure and heart rate in our patients did not change during the administration of high doses of furosemide, a redistribution of renal blood flow is likely.

During the high doses of furosemide treatment, the reduction in body weight in our patients is low. However, during the combined therapy with high doses furosemide and low dose dopamine, the reduction in body weight in these patients was enhanced by more than two-fold. This considerable reduction in body weight is accompanied by a significant decrease in serum creatinine. These favourable changes have to be based on the renal action of dopamine [20], since no direct cardiac effect of dopamine in such a low dose has been observed. The improvement in renal function may be explained by decreased renal vascular resistance and increased glomerular filtration rate. A significant increase in creatinine clearance in 5 of these patients during the combined therapy with high dose furosemide and low dose dopamine confirms the increase in glomerular filtration rate.

Levodopa, which is extensively used for treatment of Parkinson's disease [21-23], and is decarboxylated in the kidney to dopamine, increases renal plasma flow, glomerular filtration and sodium and potassium excretion of these patients [23]. The persistent natriuresis during chronic treatment with levodopa [23, 24] can be beneficial to the patients with congestive heart failure. In refractory congestive heart failure, levodopa, combined with high dose furosemide might be preferred for maintenance therapy.

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Chapter 3: Dopamine and peripheral circulation

3.1 Introduction

Essential hypertension is diagnosed when no primary cause for blood pressure elevation is identified. The primary pathogenic abnormality present in essential hypertension is not clearly identified. Blood pressure rises slowly with age either in normotensive or hypertensive subjects. However, the rate of rise of blood pressure in essential hypertension is faster than in normotensive subjects. The potential causal mechanisms, which might raise blood pressure, are:

1. Abnormal function of the sympathetic nervous system.

Although some studies have suggested that plasma levels of noradrenaline are increased in essential hypertension, this is by no means a universal finding [1-8]. Additionally, urinary catecholamine excretion, which is a reliable marker for sympathetic nervous system activity, was not elevated in a large study of subjects with mild hypertension [9].

2. Impaired renal sodium excretion.

Renal sodium excretion might be impaired in early human essential hypertension. This may result in alternatively:

a. an increase in plasma volume, which will cause an increase in cardiac output, blood pressure and tissue perfusion [10]. Body tissues have an intrinsic capacity to regulate blood flow by varying arteriolar resistance relationship with perfusion pressure. Preliminary evidence suggests that plasma concentrations of human atrial natriuretic peptide are increased in some, but not all, subjects with essential hypertension [11], supporting the concept of central volume expansion.

b. an increase in peripheral resistance by vasoconstriction [12] or a rise in resting tone in vascular smooth muscle cells [13] due to a circulating sodium transport inhibitor.

3. Altered activity of pressor and/or depressor hormones.

Although plasma renin concentration is reported to be abnormal in essential hypertension, this variable changes with age often in a direction which is inconsistent with

their having a pathogenic role in the development or maintenance of essential hypertension [9]. It has been suggested that a reduced effect of renal dopamine, which have a local action in the kidney to regulate Na excretion, might account for the abnormal sodium excretion in essential hypertension [14]. If the same is also true for the vascular system, this phenomenon might explain the increased renal and systemic vascular resistance in essential hypertensives.

Then, there must be a difference in vascular response to an increase in dopamine level between essential hypertensives and normotensives. Furthermore, the vascular response to other sympathomimetic drug might also be different between normotensives and essential hypertensives.

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3.2 Systemic haemodynamic effects of dopamine in hypertensive patients rendered normotensive after acute myocardial infarction.

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Summary

The systemic haemodynamic effects of dopamine were studied in seven hypertensive patients rendered normotensive after myocardial infarction and in seven normotensive patients with myocardial infarction. Plasma levels of noradrenaline and renin were measured before and during infusion of dopamine ($5.0 \mu\text{g/kg/min}$), and in the wash-out period. In spite of comparable increases in cardiac output in both patient groups (previous hypertensives: cardiac index from $2.64 \pm 0.14 \text{ l/min/m}^2$ to $2.99 \pm 0.13 \text{ l/min/m}^2$, $p < 0.005$ and $3.22 \pm 0.14 \text{ l/min/m}^2$, $p < 0.005$, respectively; normotensives: cardiac index from $2.83 \pm 0.13 \text{ l/min/m}^2$ to $3.17 \pm 0.18 \text{ l/min/m}^2$, $p < 0.01$ and $3.47 \pm 0.20 \text{ l/min/m}^2$, $p < 0.005$, respectively), caused by either dose of dopamine, previously hypertensive patients responded to dopamine by increasing systolic and diastolic arterial pressure (systolic arterial pressure from $125.6 \pm 7.5 \text{ mm Hg}$ to $140.9 \pm 8.6 \text{ mm Hg}$, $p < 0.005$ and $162 \pm 13.6 \text{ mm Hg}$, $p < 0.005$, respectively; diastolic arterial pressure from $66.1 \pm 1.5 \text{ mm Hg}$ to $69.6 \pm 1.2 \text{ mm Hg}$, $p < 0.05$ and $73.5 \pm 1.7 \text{ mm Hg}$, $p < 0.01$ respectively) and maintaining systemic vascular resistance (from $1491 \pm 48.4 \text{ dynes.sec.cm}^{-5}$ to $1467 \pm 30.0 \text{ dynes.sec.cm}^{-5}$, $p \text{ NS}$, and $1520 \pm 44.3 \text{ dynes.sec.cm}^{-5}$, $p \text{ NS}$, respectively), whereas normotensive patients responded by decreasing diastolic arterial pressure (from $64.8 \pm 1.6 \text{ mm Hg}$ to $61.2 \pm 2.2 \text{ mm Hg}$, $p < 0.05$ and $61.2 \pm 1.9 \text{ mm Hg}$, $p < 0.05$, respectively) and systemic vascular resistance (from $1341 \pm 81.3 \text{ dynes.sec.cm}^{-5}$ to $1183 \pm 80.7 \text{ dynes.sec.cm}^{-5}$, $p < 0.001$ and $1120 \pm 75.2 \text{ dynes.sec.cm}^{-5}$, $p < 0.001$, respectively). The difference between the former and the latter responses to dopamine may be based on the vascular hyperreactivity of previously hypertensive patients to the alpha-adrenergic receptor-stimulating property of this drug. Noradrenaline release from sympathetic nerve endings was stimulated (previous hypertensives: an increment of $0.30 \pm 0.09 \text{ ng/ml}$, $p < 0.01$; normotensives: an increment of $0.20 \pm 0.07 \text{ ng/ml}$, $p < 0.05$) and renin release was unaltered by dopamine in both patient groups.

Introduction

Dopamine, the immediate precursor of noradrenaline, stimulates myocardial contraction directly by acting on β_1 -adrenergic receptors in the myocardium and indirectly by releasing noradrenaline from sympathetic nerve terminals, which in turn stimulate β_1 -adrenergic receptors [1]. Its effects on β_2 -adrenergic receptors, which subserve vasodilatation, are minimal [1]. Dopamine also acts on alpha-adrenergic receptors in arteries and veins, and causes vasoconstriction [1]. Dopamine-induced vasodilatation, caused by activation of specific dopaminergic receptors [2, 3], occurs in the renal [4], mesenteric, coronary and cerebral vascular beds [1]. Studies in normal subjects [2] have shown that intravenous infusion of

dopamine at rates ranging from 0.5 to 2 $\mu\text{g/kg/min}$ increases renal blood flow without significant effects on cardiac contractility or heart rate. In this dose range, arterial pressure either decreases slightly or does not change. With rates of infusion ranging from 2 to 10 $\mu\text{g/kg/min}$, dopamine acts on β_1 -adrenergic receptors to increase cardiac contractility, cardiac output, and stroke volume. Usually the heart rate is not significantly altered. With faster rates of infusion, usually above 10 $\mu\text{g/kg/min}$, arterial blood pressure is increased due to action on α -adrenergic receptors.

Clinical use of dopamine in the treatment of shock has been described [5-7]. This drug has also been used in patients with cardiogenic shock following acute myocardial infarction [8, 9], and in patients early after cardiac surgery [10]. Most hypertensive patients are rendered normotensive for up to 8 weeks after myocardial infarction [11]. Moreover, the absence of increased systemic vascular resistance in the presence or absence of shock may occur after myocardial infarction [12-15]. Acute hypertensive reactions have been observed in some patients treated with dopamine, but only theoretical explanations were mentioned [16]. We therefore studied the haemodynamic effects of dopamine in hypertensive patients whose blood pressure returned to normal after acute myocardial infarction. The effects of dopamine in normotensive patients with myocardial infarction were also studied.

Patients and methods

Fourteen patients whose myocardial infarctions were documented electrocardiographically and enzymatically, who had no arrhythmia and were not on any medication, entered the study. Seven hypertensive patients (all males) ranging in age from 45 to 61 years (mean age 53 years), whose blood pressure returned to normal after acute myocardial infarction (group A) and 7 normotensive patients (1 female and 6 males) ranging in age from 30 to 63 years (mean age 57 years) with acute myocardial infarction (group B) consented to the study. Antihypertensive drugs were withdrawn on the day of admission to the coronary care unit. The study was carried out 3-7 days after the acute event, for plasma noradrenaline concentrations were back to normal 48 to 72 hours after admission in patients with uncomplicated myocardial infarction [17], and the change in heart rate had returned to the pretreatment baseline 60 to 72 hours after the last dose of a β -adrenergic receptor-blocking agent [18]. All patients of group A were treated with a β -adrenergic receptor-blocking drug and a diuretic prior to the acute event, and the mean systolic and diastolic blood pressures were 159.2 ± 7.2 mm Hg and 93.6 ± 3.4 mm Hg, respectively. Two of them showed ECG evidence of left ventricular hypertrophy and were known to have been hypertensive for more than 10 years.

ECG electrodes were placed for monitoring and recording. After inserting a catheter into a brachial artery for blood pressure recording, a triple-lumen thermodilution

Swan-Ganz catheter was introduced percutaneously into a cubital vein and placed in the pulmonary artery for measurement of cardiac output by a thermodilution technique [19]. After 30 minutes, blood samples were collected for determination of plasma noradrenaline [20] and renin [21]. Arterial pressure and ECG were then recorded and cardiac output was determined. Dopamine was infused at a rate of 2.5 $\mu\text{g/kg/min}$ during 20 minutes, followed by a rate of 5.0 $\mu\text{g/kg/min}$ during 20 minutes. The same measurements were made when a new stable state of heart rate and blood pressure was achieved during each dose of dopamine infusion. After the largest dose had been administered, a wash-out period of 30 minutes followed. At the end of this period, blood samples for determination of plasma noradrenaline and renin concentrations were collected and the haemodynamic parameters were measured again. The systemic vascular resistance and its index were calculated. Student's t-test for comparison of paired data and the t-test for independent means was used to compare the two groups. A p-value of less than 0.05 was considered to indicate a significant difference.

Results

Mean values of the haemodynamic parameters and plasma levels of noradrenaline and renin in patients of group A and group B, before, during and after continuous infusion of dopamine, are shown in table I. The mean pretreatment cardiac indices in the two groups did not differ. A dose-related, significant increase in cardiac index during both doses of dopamine infusion was observed in both groups. The absolute increments of cardiac index during each dose of dopamine infusion in both groups did not differ. The percentual increments were 11.1 ± 2.1 and 18.9 ± 3.3 in group A, and 11.6 ± 3.0 and 22.5 ± 3.0 in group B, respectively.

The mean pretreatment systolic arterial pressures in both groups did not differ significantly (fig. 1). During both doses of dopamine infusion, the systolic arterial pressure in group A rose substantially from 125.6 ± 7.5 mm Hg to 140.9 ± 8.6 mm Hg ($p < 0.005$) and 162.2 ± 13.6 mm Hg ($p < 0.005$), respectively, while a significant rise in systolic arterial pressure in group B was attained only during the larger dose of dopamine infusion (from 120.1 ± 4.7 mm Hg to 120.8 ± 5.7 mm Hg ($p > 0.05$) and 130.7 ± 7.6 mm Hg ($p < 0.05$), respectively). The mean pretreatment diastolic arterial pressure in both groups was comparable (fig. 1). During both doses of dopamine infusion, the diastolic arterial pressure in group A rose evidently from 66.0 ± 1.5 mm Hg to 69.6 ± 1.2 mm Hg ($p < 0.05$), and 73.5 ± 1.7 mm Hg ($p < 0.01$), respectively, while the diastolic arterial pressure in group B decreased significantly from 64.8 ± 1.6 mm Hg to 61.2 ± 2.2 mm Hg ($p < 0.05$) and 61.2 ± 1.9 mm Hg ($p < 0.05$), respectively. The difference between the increase (group A) and the decrease (group B) in diastolic arterial pressure during each dose of dopamine infusion attained statistical significance (group A versus group B: $+3.8 \pm 1.0$ mm Hg versus -3.6 ± 1.3

	Pretreatment			Dopamine ($\mu\text{g/kg/min}$)			Wash-out		
	2.5			5.0					
	A	B	P ₂	A	B	P ₂	A	B	P ₂
CI									
mean	2.64	2.83		2.99	3.17		3.22	3.47	
SEM	0.14	0.13	NS	0.13	0.18	NS	0.14	0.20	NS
P ₁				***	**		***	***	
MAP									
mean	85.9	82.9		93.4	81.1		103.3	84.4	
SEM	3.3	1.9	NS	3.5	2.4	X	5.6	2.9	X
P ₁				***	NS		***	NS	NS
HR									
mean	72.4	76.6		75.0	78.3		72.6	80.1	
SEM	3.9	2.3	NS	4.0	3.4	NS	3.2	5.3	NS
P ₁				NS	NS		NS	NS	NS
SVR									
mean	1491	1341		1467	1183		1520	1120	
SEM	48.4	81.3	NS	30.0	80.7	XXX	44.3	75.2	XXXX
P ₁				NS	****		NS	****	NS

A : hypertensive patients rendered normotensive after myocardial infarction; B : normotensive patients with myocardial infarction; CI : cardiac index (litre/min/m²); MAP : mean arterial pressure (mm Hg); HR : heart rate (beats/min); SVR : systemic vascular resistance (dynes.sec.cm⁻⁵)

P₁ (paired Student's t-test): * : p<0.05; ** : p<0.01; *** : p<0.005; **** : p<0.001

P₂ (unpaired Student's t-test): X : p<0.05, XX : p<0.01, XXX : p<0.005, XXXX : p<0.001

Table 1.

Mean haedodynamic parameters in patiënts with acute myocardial infarction before, during and after dopamine infusion.

Fig. 1. The effects of 2.5 and 5.0 $\mu\text{g/kg/min}$ dopamine on systolic and diastolic arterial pressure and systemic vascular resistance index. (□): hypertensive patients rendered normotensive after myocardial infarction, (■): normotensive patients with myocardial infarction, C: pretreatment, WO: wash-out period, AP: arterial pressure (mm Hg), SVRI: systemic vascular resistance index (dynes.sec.cm⁻⁵m²), *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.005$.

mm Hg [$p < 0.01$] and $+8.0 \pm 0.8$ mm Hg versus -3.6 ± 1.7 mmHg ($p < 0.005$), respectively.

The difference in pretreatment mean arterial pressure between the two groups did not attain statistical significance (table 1). During the infusion of both doses of dopamine, the mean arterial pressure in group A increased significantly by 10.0 ± 1.6 per cent and 22.2 ± 1.8 per cent, respectively, while the mean arterial pressure in group B did not change significantly. The difference between the increase (group A) and the change (group B) in mean arterial pressure during infusion of each dose of dopamine attained statistical significance.

The pretreatment heart rates in the two groups did not differ significantly. No significant increases in heart rate during both doses of dopamine infusion were observed in either group.

The difference in mean pretreatment systemic vascular resistance between the two groups did not attain statistical significance. During infusion of both doses of dopamine, the changes in systemic vascular resistance in group A were not statistically significant, while the reduction in systemic vascular resistance in group B were marked. The difference between the change (group A) and the reduction (group B) in systemic vascular resistance during each dose of dopamine infusion attained statistical significance (group A versus group B: -24 ± 22.9 dynes.sec.cm⁻⁵ versus -158 ± 26.3 dynes.sec.cm⁻⁵, $p < 0.005$ and $+30 \pm 20.5$ dynes.sec.cm⁻⁵ versus -221 ± 40.6 dynes.sec.cm⁻⁵, $p < 0.0005$, respectively).

During dopamine infusion, similar changes in the systemic vascular resistance index and in systemic vascular resistance were observed in both groups (fig. 1).

The pretreatment plasma noradrenaline concentrations in the two groups did not differ significantly (fig. 2). During $5.0 \mu\text{g/kg/min}$ of dopamine infusion, the plasma noradrenaline concentration in group A rose significantly from 0.26 ± 0.02 ng/ml to 0.56 ± 0.08 ng/ml ($p < 0.01$) and the plasma noradrenaline concentration in group B rose evidently from 0.37 ± 0.06 ng/ml to 0.57 ± 0.06 ng/ml ($p < 0.05$). Although the rise in plasma noradrenaline concentration during dopamine infusion was higher in group A (0.30 ± 0.09 ng/ml) than in group B (0.20 ± 0.07 ng/ml), the difference did not attain statistical significance. The mean pretreatment plasma renin concentrations in the two groups did not differ significantly (fig. 2). During $5.0 \mu\text{g/kg/min}$ of dopamine infusion, there were no significant changes in plasma renin concentration in both groups (group A: from 9.3 ± 1.8 ng AI/ml.h to 10.5 ± 2.2 ng AI/ml.h; group B: from 15.3 ± 3.9 ng AI/ml.h to 14.9 ± 3.5 ng AI/ml.h). During the wash-out period all the parameters returned to the pretreatment values and did not differ significantly from the latter (table 1 and figs. 1 and 2).

Fig. 2.
The effect of 5.0 $\mu\text{g/kg/min}$ dopamine on plasma levels of noradrenaline and renin. PNC: plasma noradrenaline concentration (ng/ml), PRC: plasma renin concentration (ng AI/ml.h). *: $p < 0.05$, **: $p < 0.01$. See fig. 1 for other abbreviations.

Discussion

In this study, the enhancements in cardiac index during either dose of dopamine infusion in group A and in group B were comparable. In spite of these similar increases in cardiac output, the systolic and diastolic arterial pressure in group A rose significantly during both doses of dopamine infusion, whereas the systolic arterial pressure in patients of group B rose significantly only during the second dose of dopamine administration and their diastolic arterial pressure decreased evidently during both doses of dopamine infusion. These incomparable changes in blood pressure were based on the insignificant changes in systemic vascular resistance in group A and the marked reductions in systemic vascular resistance in group B during both doses of dopamine infusion. These different changes in systemic vascular resistance

denote that the dopaminergic receptor-stimulating property of dopamine, which dilates the renal, mesenteric, coronary and cerebral vascular beds [2, 3], is counteracted by its vasoconstrictor effect in patients in group A, whereas its vasodilator effect in group B predominates its vasoconstrictor alpha-adrenergic receptor-stimulating property. If this is true, it means that hypertensive patients rendered normotensive after myocardial infarction, show vascular hyperreactivity to the alpha-adrenergic receptor-stimulating property of dopamine. Vascular hyperreactivity to vasoconstrictor substance has been described in hypertensive patients [22-24]. The significant difference between the change in systemic vascular resistance in group A and that in group B during each dose of dopamine infusion is not explained solely by the greater, but insignificant [$p > 0.1$], release of endogenous noradrenaline in group A than in group B. The insignificant changes in heart rate during both doses of dopamine infusion in both groups confirmed the results of others [25-27].

The rise in plasma noradrenaline concentration during dopamine infusion in both groups supports the finding of Nash et al. [28]. The insignificant changes in plasma renin concentration during the second dose of dopamine infusion in both groups may indicate that the overall effect of $5.0 \mu\text{g/kg/min}$ dopamine infusion in 20 minutes on renin release in man is not apparent. This finding is in agreement with previous reports on an insignificant change in plasma renin activity during a small dose ($3-6 \mu\text{g/kg/min}$) of dopamine infusion [29]. The significant rise in renin level during infusion of a larger dose of dopamine in animal [29] and man [30] may be explained mainly by its beta-adrenergic receptor-stimulating property, which stimulates the renal beta-adrenergic receptor [29]. Dopamine infusion exceeding $1 \mu\text{g/kg/min}$ causes consistent natriuresis [1], and prolonged administration of this drug without sufficient sodium replacement may cause volume and sodium depletion. The reported increase in plasma renin activity during $3.0 \mu\text{g/kg/min}$ or prolonged dopamine infusion [31] may be due to sodium depletion [32], caused by prolonged natriuresis.

Dopamine has been used in critical care patients of various types [35-39]. Since the changes in clinical variables related to the state of acute illness may mask underlying hypertension, care must be taken to adjust the infusion rate carefully to prevent an excessive increase in peripheral resistance.

Acknowledgements

We wish to thank Prof. W.H. Birkenhäger and X.H. Krauss for their advice and Mr. Kret, Clin. Midy, for supplies of dopamine [Intropin]. We are indebted to Ms. A.T. Erwich, L. Baar and J. Moor for their technical assistance.

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3.3 Cardiovascular effects of dobutamine in hypertensive patients whose blood pressure returned to normal after acute myocardial infarction.

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Summary

The haemodynamic effects of dobutamine were studied in 7 hypertensive patients whose blood pressure returned to normal after acute myocardial infarction and in 7 normotensive patients with myocardial infarction. Renin and noradrenaline levels in plasma were measured before and during the larger dose of dobutamine infusion, and in the wash-out period. Hypertensive patients whose blood pressure returned to normal after acute myocardial infarction responded to dobutamine infusion by a marked increase in arterial pressure and systemic vascular resistance (systolic arterial pressure in mm Hg: from 120.9 ± 7.5 to 151.4 ± 11.8 ($p < 0.01$) and 168.1 ± 12.3 ($p < 0.005$), respectively; diastolic arterial pressure in mm Hg: from 63.1 ± 2.7 to 71.8 ± 2.9 ($p < 0.05$) and 78.5 ± 3.1 ($p < 0.005$), respectively; systemic vascular resistance index in dynes.sec.cm⁻⁵.m²: from 2594 ± 103.6 to 2916 ± 147.4 ($p < 0.05$) and 3060 ± 175.1 ($p < 0.01$), respectively), which may be based on a higher vasopressor response to the alpha-adrenergic receptor-stimulating property of this drug. The increase in cardiac output was therefore restricted (cardiac index in l/min/m²: from 2.54 ± 0.10 to 2.69 ± 0.11 ($p < 0.05$) and 2.87 ± 0.17 ($p < 0.01$), respectively). Despite the obvious increase in baroreceptor reflex depressor activity evoked by the increased blood pressure, the chronotropic property of dobutamine was still apparent during the larger dose of infusion. Normotensive patients with acute myocardial infarction responded to dobutamine by a pronounced increase in cardiac output and heart rate (cardiac index in l/min/m²: from 2.79 ± 0.21 to 3.28 ± 0.17 ($p < 0.01$) and 3.54 ± 0.21 ($p < 0.01$), respectively; heart rate in beats/min: from 76.1 ± 4.4 to 85.9 ± 5.2 ($p < 0.005$) and 94.4 ± 6.0 ($p < 0.005$), respectively), and by a decrease in systemic vascular resistance (systemic vascular resistance index in dynes.sec.cm⁻⁵.m²: 2395 ± 176.3 to 2077 ± 125.9 ($p < 0.05$) and 1935 ± 126.8 ($p < 0.05$), respectively); this may be due to dilatation of skeletal muscle vascular beds. Noradrenaline level, as an index of sympathetic tone, was reduced (previous hypertensives: from 0.29 ± 0.07 ng/ml to 0.12 ± 0.03 ng/ml ($p < 0.005$); normotensives: from 0.43 ± 0.05 ng/ml to 0.35 ± 0.06 ng/ml ($p < 0.005$) and renin release was stimulated (plasma renin concentration in ng AI/ml.h: in previous hypertensives: from 8.8 ± 2.2 to 11.6 ± 2.2 ($p < 0.005$); in normotensives: from 13.7 ± 3.9 to 17.1 ± 4.3 ($p < 0.05$), respectively) by dobutamine in both patient groups.

Introduction

Dobutamine is a cardioactive sympathomimetic amine that stimulates beta₁-, beta₂ and alpha-adrenergic receptors [1, 2] Although the chemical structures of dobutamine and dopamine are very similar, the former does not stimulate dopaminergic receptors [1] [fig. 1]. It has been observed by some investigators [3-7] that dobuta-

D O P A M I N E

D O B U T A M I N E

Fig. 1. Chemical formula of dopamine and dobutamine.

mine has fewer chronotropic and dysrhythmogenic effects than isoproterenol, while the effects on cardiac output are comparable. In experimental myocardial infarction in dogs, dobutamine (unlike isoproterenol) increases the oxygen content of coronary sinus blood and does not increase the infarct size [8]. It should therefore be beneficial in patients with acute myocardial infarction and impaired contractility. Clinical studies on the effect of dobutamine in patients with acute myocardial infarction have been carried out with various aims [9-12] Astrup et al. [13] reported that blood pressure returned to normal after myocardial infarction in 37 of 58 hypertensive patients and remained normal for up to 8 weeks. Other investigators [12] observed a pronounced increase in blood pressure during dobutamine infusion in some of their hypertensive patients, but no haemodynamic explanations were given.

The question arises whether the cardiac or the vascular response to dobutamine in hypertensive patients differs from that in normotensive patients. We therefore studied the haemodynamic effects of dobutamine in hypertensive patients whose blood pressure returned to normal after acute myocardial infarction, before, during and after infusion of dobutamine. The haemodynamic effects of dobutamine in normotensive patients with acute myocardial infarction were also studied.

Patients and methods

Fourteen patients whose myocardial infarctions were documented electrocardiographically and enzymatically, were divided into two groups according to their history and clinical data on hypertension or normotension prior to the acute event. Group A consisted of 7 men with a mean age of 53 years (range 45 to 61 years), known to have had essential hypertension, whose blood pressure returned to normal after acute myocardial infarction, and group B consisted of one woman and 6 men with a mean age of 57 years [range 30 to 63 years], known to have had normal blood pressure before the acute event. All patients of group A were treated with a beta-adrenergic receptor-blocking agent and a diuretic prior to the acute event, and the mean systolic and diastolic pressures were 159.2 ± 7.2 mm Hg and 93.6 ± 3.4 mm

Hg, respectively. Two of them showed ECG evidence of left ventricular hypertrophy and were known to have had hypertension for more than 10 years. Antihypertensive drugs were withdrawn on the day of admission to the coronary care unit. None of the 14 patients had arrhythmia and none was receiving any medication.

The study was carried out 3-7 days after the acute event, for plasma noradrenaline concentrations were back to normal values 48 to 72 hours after admission in patients with uncomplicated myocardial infarction [14], and the changes in cardiac contractility and heart rate had returned to the pretreatment baseline 60 to 72 hours after the last dose of beta-adrenergic receptor-blocking agent [15]. Informed consent was obtained prior to each study. ECG electrodes were placed for monitoring and recording. After inserting a catheter into a brachial artery for blood pressure recording, a triple-lumen thermodilution Swan-Ganz catheter was introduced percutaneously into the cubital vein and placed in the pulmonary artery for measurement of cardiac output by thermodilution technique [16]. After 30 minutes, blood samples were collected for determination of plasma renin [17] and noradrenaline [18]. Arterial pressure and ECG were then recorded and cardiac output was determined.

Using an infusion pump, dobutamine was administered at a rate of $2.5 \mu\text{g/kg/min}$ during 20 minutes, followed by $5.0 \mu\text{g/kg/min}$ during 20 minutes. The same measurements were made when a new stable state of heart rate and blood pressure was achieved during each dose of dobutamine infusion. After the largest dose had been administered, a wash-out period of 30 minutes followed. At the end of this period, blood samples for determination of plasma renin and noradrenaline concentrations were collected and the haemodynamic parameters were measured again. The systemic vascular resistance index was calculated by dividing (mean arterial pressure $\times$ 80) by cardiac index, since the mean right atrial pressure was relatively low and its changes during dobutamine infusion were not significantly different from the pretreatment value [19].

Student's t-test was used for comparison of paired data and the t-test for independent means was used to compare the two groups. A p-value of less than 0.05 was considered to indicate a significant difference.

Results

Tables I and II show the mean values of the haemodynamic parameters and plasma levels of renin and noradrenaline in patients of group A and of group B, respectively, before, during and after continuous infusion of dobutamine. Although the mean pretreatment cardiac index in group A was lower than that in group B, the difference was not statistically significant. A gradual but significant increase in cardiac index during infusion of both doses of dobutamine was observed in both groups. The percentual increments were 5.7 ± 1.8 and 12.7 ± 4.8 in group A and 19.5 ± 5.1 and 29.3 ± 8.9 in group B, respectively.

Table 1. Haemodynamic parameters and plasma levels of renin and noradrenaline in hypertensive patients whose blood pressure returned to normal after acute myocardial infarction, before, during and after dobutamine infusion.

	Pretreatment	Dobutamine		Wash-out
		2.5 ($\mu\text{g/kg/min}$)	5.0 ($\mu\text{g/kg/min}$)	
CI				
mean	2.54	2.69	2.87	2.60
SEM	0.10	0.11	0.17	0.12
p		*	*	NS
SAP				
mean	120.9	151.4	168.1	124.2
SEM	7.5	11.8	12.3	7.4
p		**	***	NS
DAP				
mean	63.1	71.8	78.5	66.8
SEM	2.7	2.9	3.1	1.7
p		*	***	NS
HR				
mean	72.0	73.4	84.6	71.7
SEM	3.9	3.8	1.8	3.4
p		NS	*	NS
PRC				
mean	8.8		11.6	9.2
SEM	2.2		2.2	1.9
p			***	NS
PNC				
mean	0.29		0.12	0.24
SEM	0.07		0.03	0.03
p			***	NS

CI	: cardiac index	: l/min/m ²
SAP	: systolic arterial pressure	: mm Hg
DAP	: diastolic arterial pressure	: mm Hg
HR	: heart rate	: beats/min
PRC	: plasma renin concentration	: ng AI/ml/h
PNC	: plasma noradrenaline concentration	: ng/ml
*	: p < 0.05	
**	: p < 0.01	
***	: p < 0.005	

Table 2. Haedonomic parameters and plasma levels of renin and noradrenaline in normotensive patients with acute myocardial infarction before, during and after dobutamine infusion.

	Pretreatment	Dobutamine		Wash-out
		2.5	5.0	
		(µg/kg/min)		
CI				
mean	2.79	3.28	3.54	2.95
SEM	0.21	0.17	0.21	0.18
p		**	**	NS
SAP				
mean	116.8	126.7	127.1	122.2
SEM	4.0	4.0	5.5	5.5
p		*	*	NS
DAP				
mean	62.8	62.3	62.1	64.9
SEM	2.3	2.5	2.6	1.7
p		NS	NS	NS
HR				
mean	76.3	85.9	94.4	80.4
SEM	4.4	5.2	6.0	2.3
p		***	***	NS
PRC				
mean	13.7		17.1	14.8
SEM	3.9		4.3	3.8
P			*	NS
PNC				
mean	0.43		0.35	0.38
SEM	0.05		0.06	0.04
p			***	NS

CI : cardiac index : l/min/m²
 SAP : systolic arterial pressure : mm Hg
 DAP : diastolic arterial pressure : mm Hg
 HR : heart rate : beats/min
 PRC : plasma renin concentration : nl AI/ml/h
 PNC : plasma noradrenaline concentration : ng/ml
 * : p < 0.05
 ** : p < 0.01
 *** : p < 0.005

A similar mean pretreatment systolic arterial pressure was found in both groups. The significant increments in systolic arterial pressure during dobutamine infusion were more pronounced in group A than in group B: 25.4 ± 6.6 per cent and 39.5 ± 7.3 per cent in group A and 8.7 ± 2.3 per cent and 9.1 ± 3.0 per cent in group B, respectively. A comparable mean pretreatment diastolic arterial pressure was observed. A dose-related increase in diastolic arterial pressure during dobutamine infusion was obtained in group A, with significant increases of $14.5 \pm 5.0\%$ and $25.2 \pm 5.2\%$, whereas no significant changes in diastolic arterial pressure during dobutamine infusion occurred in group B. The mean pretreatment arterial pressures in the two groups did not differ significantly (fig. 2). During infusion of both doses of dobutamine, the mean arterial pressure in group A rose from 82.4 ± 4.0 mm Hg to 97.9 ± 5.8 mm Hg ($p < 0.05$) and 108.4 ± 5.8 mm Hg ($p < 0.005$), respectively, while that in group B did not change significantly (from 80.8 ± 1.8 mm Hg to 83.8 ± 1.9 mm Hg and 83.8 ± 2.0 mm Hg).

The mean pretreatment heart rates in the two groups did not differ significantly. The only (but significant) increase in heart rate during the larger dose of dobutamine infusion was observed in group A, whereas a dose-related and substantial increase in heart rate during infusion of both doses of dobutamine was obtained in group B. The mean pretreatment systemic vascular resistance indices in the two groups did not differ significantly (fig. 3). The systemic vascular resistance index in group A increased from 2594 ± 103.6 dynes.sec.cm⁻⁵.m² to 2916 ± 147.4 dynes.sec.cm⁻⁵.m² ($p < 0.05$) and 3060 ± 175.1 dynes.sec.cm⁻⁵.m² ($p < 0.01$), respectively, during infusion of both doses of dobutamine, whereas that in group B decreased from 2395 ± 176.3 dynes.sec.cm⁻⁵.m² to 2077 ± 125.9 dynes.sec.cm⁻⁵.m² ($p < 0.05$) and 1935 ± 126.8 dynes.sec.cm⁻⁵.m² ($p < 0.05$), respectively, during the same doses of dobutamine infusion.

Fig. 2. The mean arterial pressure before, during and after infusion of dobutamine. □ = hypertension; ■ = normotension.

Fig. 3. The systemic vascular resistance index before, during and after dobutamine infusion.

Although the pretreatment plasma renin concentration in group A was lower than that in group B, the difference did not attain statistical significance. A significant increase in plasma renin concentration was observed during the larger dose of dobutamine in both groups, the increments being 44.9 ± 13.0 per cent in group A and 31.3 ± 10.9 per cent in group B. The pretreatment plasma noradrenaline concentration was lower in group A than in group B, but the difference was not statistically significant. A significant reduction in plasma noradrenaline concentration was obtained during the larger dose of dobutamine infusion in both groups, the decreases being 52.0 ± 9.9 per cent in group A and 21.9 ± 7.2 per cent in group B.

Discussion

In this study, the increase in cardiac output by dobutamine was less pronounced in group A than in group B. The marked increase in systolic and diastolic arterial pressure in patients of group A on dobutamine, which acts as after-load, may be the explanation. The increase in systolic arterial pressure with little change in diastolic arterial pressure in patients of group B on dobutamine is comparable with the results of Waagstein et al. [12] and may be partly due to the rise in plasma renin. An increase in systolic blood pressure by 50 mm Hg or more has been reported in about 7.5 per cent of patients during dobutamine infusion [2], but dosage reduction usually reverses this effect promptly.

The heart rate was less increased by dobutamine in group A than in group B; this may be due to baroreceptor reflex depressor activity evoked by the increase in blood pressure. The significant increase in heart rate during the larger dose of dobutamine infusion in group A, in spite of the further increase in blood pressure, may be interpreted as an overriding of the baroreceptor reflex depressor activity by the

chronotropic property of the drug. The pronounced increase in heart rate caused by dobutamine in group B is mostly due to the chronotropic property of this drug, and confirms the results of others [4, 20, 21]. However, dobutamine in combination with cardiac glycosides does not increase the heart rate [19, 22-27].

The alpha-adrenergic receptor stimulating property of dobutamine [1, 2] caused a significant enhancement of systemic vascular resistance in patients of group A, but not in patients of group B; this may be based on vasopressor hyperresponsiveness. Vascular hyperreactivity to the alpha-adrenergic receptorstimulating property of catecholamines has been demonstrated in hypertensive patients [28-31]. The substantial decrease in systemic vascular resistance index in patients of group B on dobutamine may be explained by dilatation of skeletal muscle vascular beds, but not of the renal arteries [7, 32, 33].

The substantial rise in plasma renin concentration during dobutamine infusion in both groups indicates that this drug acts strongly on beta-adrenergic receptors of the juxtaglomerular apparatus, for renal blood flow does not change at all [33]. The significant reduction in plasma noradrenaline concentration by dobutamine in both groups may be an expression of a reflex reduction in sympathetic tone.

Our results indicate that dobutamine increases systemic vascular resistance in hypertensive patients whose blood pressure returned to normal after acute myocardial infarction. This may explain the marked increase in blood pressure. Since dobutamine is also used in critical care patients [5, 34-37], history and clinical data on patients of this kind can be instructive. If dobutamine is needed in hypertensive patients who for some reason have become hypotensive, it should be started in a small dose, which is then increased cautiously.

Acknowledgements

We wish to thank Prof. W.H. Birkenhäger and X.H. Krauss for their advice and Dr. DeBruyne, Lilly, Brussels, for supplies of dobutamine. We are indebted to Ms. L. Baar, J. Moor and A.T. Erwich for their technical assistance.

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Chapter 4: Dopamine and the adrenal gland

4.1 Introduction

The prevalence of primary hyperaldosteronism might be low (0.5%)[1], but an adequate screening test for this disorder is not yet available. Heart attacks and cerebrovascular accidents occur in 23% of 136 patients with primary hyperaldosteronism [2], thereby, blood pressure of equal to or higher than 180/100 mmHg has been found in more than two third of untreated patients with this disorder [3, 4]. Although hypokalemia and low plasma renin activity characterize primary hyperaldosteronism [5, 6], normal levels of potassium and renin have been found in one-fourth to one-third of untreated patients with this disorder [2-4]. Moreover about one-third of essential hypertensives has low plasma renin activity.

Exogenous dopamine does not reduce the basal secretion of aldosterone in normotensives and essential hypertensives [7]. The basal secretion of aldosterone in primary hyperaldosteronism, however, can be reduced by exogenous dopamine [7]. Plasma levels of dopamine are higher in patients with primary hyperaldosteronism compared to essential hypertensives [8]. These findings denote that endogenous dopamine maximally inhibit the basal secretion of aldosterone in normotensives and essential hypertensives, but not in patients with primary hyperaldosternism. The difference may conceivably be related to abnormality in the dopaminergic regulation of aldosterone secretion. Furthermore, the consistent increase in plasma aldosterone concentration observed in humans after metoclopramide administration have been attributed to its dopamine antagonistic effect [9-13], since participation of no other known stimulus could be demonstrated. Studies on the response of plasma aldosterone to metoclopramide in primary hyperaldosteronism have been reported [14-17], but the results are conflicting. This is the reason of the present study.

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4.2 The effect of a dopamine antagonist on plasma aldosterone in essential hypertensives and in patients with primary hyperaldosteronism before and after surgery.

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Summary

The effects of 0,08 mg/kg body weight metoclopramide, a dopamine antagonist, on the plasma aldosterone concentration and plasma renin activity were studied in 10 essential hypertensives (group I), in 9 patients with primary hyperaldosteronism (group II), and in 5 patients after removal of an aldosterone-producing adenoma, 3-6 months after surgery (group III).

6 Weeks prior to the present study, all groups were on a diet containing 120 meq sodium/day and group I and II were treated with 20 mg amiloride daily.

Before intravenous administration of metoclopramide, serum potassium, sodium and creatinine as well as urinary sodium excretion were comparable in all the three groups. The increase of plasma aldosterone in group II and group III after metoclopramide were comparable and were significantly lower than that in group I, indicating a hyporesponsiveness to dopaminergic inhibition in patients with primary hyperaldosteronism. The individual percentage responses of aldosterone in group I and group II did not overlap each other which might suggest that this test could be applied to screen hypertensive patients from primary hyperaldosteronism. Plasma renin activity was similar in all the three groups and did not significantly change following metoclopramide.

Introduction

The plasma aldosterone levels in patients with primary aldosteronism can be influenced by ACTH [1-7], angiotensin II [8, 9], potassium [10], and dopamine [11]. The basal secretion of aldosterone in patients with primary aldosteronism can be reduced by the administration of exogenous dopamine, but not in patients with essential hypertension and normotensive controls [11]. Metoclopramide, a dopamine antagonist, acutely increases basal aldosterone secretion in normal man [12-14], in hypopituitary and bilaterally nephrectomised man [15], and has no effect on the metabolic clearance rate of aldosterone stimulating peptide [16]. Conflicting results [17-19] of the response of plasma aldosterone to metoclopramide have been reported in patients with primary hyperaldosteronism. The discrepancy may partly be explained by the dexamethasone pretreatment in one of the studies, since dexamethasone has been shown to increase plasma dopamine levels in patients with primary hyperaldosteronism [20]. Furthermore, hypokalemia directly suppresses aldosterone biosynthesis, even from an adenoma; plasma aldosterone levels may seem therefore to be normal in hypokalemic patients with primary hyperaldosteronism [10].

The aim of the present study is to investigate the influence of endogenous dopamine on the plasma aldosterone levels in essential hypertensives and in patients with

primary hyperaldosteronism, during oral treatment with the potassium sparing diuretic, amiloride [21, 22]. Patients in whom an aldosterone-producing adenoma was removed 3 to 6 months before, were also studied.

Patients and methods

Twenty four patients consented for the study; 10 patients with essential hypertension (group I), 9 patients with primary hyperaldosteronism (group II) and 5 patients after surgical removal of an aldosterone-producing adenoma (group III).

Group I included 8 females and 2 males, ranging in age from 38 to 63 years (mean 54 ± 3 years). The diagnosis of essential hypertension was based on normal serum electrolytes and creatinine, normal urinary excretion of vanilylmandelic acid, 17-OH corticosteroid and cortisol, rapid sequence urography, and plasma aldosterone-renin ratio of less than 400 in a recumbent position and during the oral treatment with amiloride [23].

Group II included 7 females and 2 males, ranging in age from 44 to 63 years (mean 51 ± 4 years). The diagnosis of primary hyperaldosteronism was based on plasma aldosterone-renin ratio of more than 400 in a recumbent position and during the oral treatment with amiloride [23], and the demonstration of an adrenal lesion by computed tomography [24-26] and adrenal vein sampling for aldosterone estimation.

Group I and group II were treated with amiloride, 20 mg daily, for at least 6 weeks prior to the study.

Group III included 4 females and 1 male, ranging in age from 52 to 63 years (mean 59 ± 3 years). They were not on medication.

All of the three patient groups had normal renal function.

After the insertion of a catheter into a cubital vein and followed by at least 60 minutes of recumbency, blood samples for the assay of plasma renin activity [27], and aldosterone concentration [28] were obtained at 9:30 A.M. Then, 0.08 mg/kg metoclopramide was intravenously administered. After 15 minutes had been elapsed, blood samples were collected for the same purpose. Thereafter, a second 0.08 mg/kg metoclopramide was given intravenously and after 15 minutes blood samples were collected again for the same purpose. The study was carried out at an outpatient clinic.

Statistical analysis was accomplished by use of student t-test within groups and the t-test for independent means was used to compare between groups. A 2p-value for paired data and a p-value for unpaired data of less than 0.05 was considered to indicate a significant difference.

Results

Table I gives the mean s.e.m. of blood pressure, levels of serum potassium, sodium, creatinine and 24-hour urinary sodium excretion in group I and group II, during oral treatment with amiloride and in group III, 3-6 months after surgery and not on any medication. There was no significant difference in blood pressure, serum potassium, sodium, creatinine, and 24-hour urinary sodium excretion between group I and group II.

A significant difference was found between group II and group III for their systolic blood pressure ($164,3 \pm 6,7$ mmHg vs $143,5 \pm 2,0$ mmHg, $p < 0,05$), but not for their diastolic blood pressure. Comparing the systolic blood pressure of the 5 patients studied before and after surgery, there was also a significant difference. There was no significant difference in blood pressure between group I and group III. No significant difference in biochemical values among patient groups, one to each other, was observed.

Fig. I shows the individual values of plasma aldosterone concentration in group I and group II, during amiloride therapy, and in group III, before and after the administration of the first and the second dose of metoclopramide. The basal values of group I and those of group II overlapped each other.

Table II gives the mean $\pm$ s.e.m. of plasma aldosterone and plasma renin activity in the three groups, before and after both gifts of metoclopramide.

The mean plasma aldosterone concentration in group I rose markedly and significantly after both gifts of metoclopramide. The mean percentage increments were 102,5% after the first gift and 153,7% after the second gift, respectively. Plasma aldosterone concentration in group II tended to increase, but not significantly, after the first gift, then increased significantly after the second gift of metoclopramide, the increments being 13,4% and 22,6%, respectively. Plasma aldosterone concentration in group III increased after both gifts of metoclopramide, the increment being 40,8% and 58,7%, respectively. Comparing the increases in plasma aldosterone concentration, after the first gift of metoclopramide in group I and group II, revealed a significant difference ($8,3 \pm 2,1$ ng/100 ml vs $3,5 \pm 1,5$ ng/100 ml, $p < 0,05$). This difference became more obvious after the second gift of metoclopramide ($11,3 \pm 1,9$ vs $5,9 \pm 1,6$ ng/100 ml, $p < 0,025$). Comparing the increases in plasma aldosterone, after the first gift of metoclopramide, between group I and group III, revealed also a significant difference ($8,3 \pm 2,1$ ng/100 ml vs $3,0 \pm 0,8$ ng/100 ml, $p < 0,05$). This difference became more substantial after the second gift of metoclopramide ($11,3 \pm 1,9$ ng/100 ml vs $4,5 \pm 1,3$ ng/100 ml, $p < 0,05$). Comparing the increases in plasma aldosterone concentration, after the first and the second gift of metoclopramide, between group II and group III, there was no significant difference ($3,5 \pm 1,5$ ng/100 ml vs $3,0 \pm 0,8$ ng/100 ml, $p > 0,40$ and $5,9 \pm 1,6$ ng/100 ml vs $4,5 \pm 1,3$ ng/100 ml, $p > 0,25$). No significant difference in plasma renin activity, before the gift of metoclopramide, among the three groups, one to each other,

Table 1. Mean $\pm$ s.e.m. of hemodynamic and biochemical values.

	BP		Serum levels			Urinary
	mmHg		K +	Na +	Creatinine	Na + excretion
	syst.	diast.	mmol/l	mmol/l	μ mol/l	mmol/24 h
EHT						
mean	115.0	98.3	4.5	141.5	76.0	123.2
s.e.m.	10	4.6	0,1	0,6	4,6	17,5
PA						
mean	164.3	104.9	4.5	139.6	82.4	125.0
s.e.m.	6,7	4,8	0,1	1,3	5,3	15,0
APA						
mean	143.5	95.0	4.4	139.5	81.0	102.5
s.e.m.	2,0	2,0	0,1	1,6	4,3	10,4

EHT (Group I) : patients with essential hypertension during treatment.

PA (group II) : patients with primary hyperaldosteronism during treatment.

APA (Group III) : patients with surgically removed aldosterone-producing adenoma.

Table 2. Mean $\pm$ s.e.m. of plasma aldosterone concentration (PAC) and renin activity (PRA) before and after 0,08 mg/kg BW metoclopramide i.v.

—	Before	after	
		1st dose	2nd dose
<hr/>			
<i>PAC ng/10 ml</i>			
EHT	8,6 ± 2,1	16,9 ± 3,9**	19,9 ± 3,9***
PA	27,7 ± 2,6	31,2 ± 3,2	33,6 ± 3,3*
APA	7,2 ± 1,2	10,2 ± 1,9*	11,7 ± 2,5*
 <i>PR ng AI/ml.h</i>			
EHT	0,36 ± 0,08	0,39 ± 0,09	0,43 ± 0,11
PA	0,37 ± 0,06	0,34 ± 0,07	0,32 ± 0,06
APA	0,56 ± 0,12	0,60 ± 0,12	0,66 ± 0,13

* p < 0,05

** p < 0,01

*** p < 0,005

was observed. No significant alterations in plasma renin activity within the groups, after the repetitive administration of metoclopramide, were observed.

Fig. 1

Fig. 2.

Fig. II shows the individual increments in percentage of plasma aldosterone in the three groups after the intravenous administration of both doses of metoclopramide. The mean percentage increments of plasma aldosterone in group I, after both gifts of metoclopramide was $153.7 \pm 28.0\%$ (range from 100 to 290%), whereas the mean percentage increments of plasma aldosterone in group II after both gifts of metoclopramide was $22.6 \pm 6.0\%$ (range from 1,1 to 40,9%). The mean percentage increments of plasma aldosterone in group III after both gifts of metoclopramide was $58.7 \pm 11.3\%$ (range from 22,8 to 77%). There was a significant difference in mean percentage increments of plasma aldosterone between group I and group II ($p < 0,001$) and between group II and group III ($p < 0,01$).

Discussion

The percentage increments of plasma aldosterone in essential hypertensives (group I) are greater than those in patients with hyperaldosteronism (group II) after both gifts of metoclopramide. In patients with primary hyperaldosteronism, the response is variable, some show an increase up to 40% while others showing no increase. This finding explains the apparent conflicting results from the literature where a presence or absence of a response of plasma aldosterone to metoclopramide in primary hyperaldosteronism have been reported [17, 18]. The percentage increments of plasma aldosterone to metoclopramide, in group I and in group II, do not overlap each other (Fig. II), and the mean increases in plasma aldosterone concentration in group I and in group II, do differ significantly from each other. These findings denote that, in comparison with the response to metoclopramide in essential hypertensives, patients with primary hyperaldosteronism have an aldosterone hyporesponsiveness to metoclopramide. Our results are in contrast to the finding of Gniadek et al. [19], which demonstrate a hyperresponsiveness of aldosterone to metoclopramide in primary aldosteronism. Their patients have been treated with dexamethasone, 2 mg daily for 3 days prior to the study, which may explain the insignificant difference between their patients and the controls in the mean plasma aldosterone concentration before the administration of metoclopramide, and the marked increase in plasma aldosterone thereafter, since dexamethasone has been shown to increase plasma dopamine levels in patients with primary hyperaldosteronism [20]. On the contrary our patients were pretreated with amiloride for 6 weeks. The percentage increments of plasma aldosterone to metoclopramide in patients after surgical removal of aldosterone-producing adenoma (group III) and in group II do overlap each other, but do not overlap with the percentage increments of plasma aldosterone to metoclopramide in group I. It is unknown why the percentage increments of plasma aldosterone level after metoclopramide was still blunted in the patients, in whom 3-6 months after an aldosterone-producing adenoma was removed compared to those in patients with essential hypertension. Several possibilities should be investigated.

The role of amiloride on the response of aldosterone level to metoclopramide could be studied before and after amiloride pretreatment, this was not reported up to now. Alternatively, it is conceivable that the response of aldosterone to metoclopramide in patients after surgical removal of aldosterone-producing adenoma should take time to reach a normal pattern; repeated metoclopramide studies over time after the removal of adenoma has not been published up to now. Kuchel et al. [29] have demonstrated, that patients with aldosterone-producing adenoma preoperatively have a significantly higher plasma dopamine concentration than postoperatively. This may explain the significant difference between group II and group III in the percentage increments of plasma aldosterone after both gifts of metoclopramide. The plasma renin activity does not change after metoclopramide in either one of the three groups. This confirms the results of others [13, 15, 19].

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Chapter 5: Dopamine and the kidney

5.1 Introduction

Whereas the results of clinical organ transplantation, using cyclosporine as the major immunosuppressive drug, have been encouraging [1-9], a serious problem of nephrotoxicity has emerged [9-12]. From the studies on cyclosporine in patients, reduced renal plasma flow and glomerular filtration rate [13-15], increased renal vascular resistance [16], low plasma renin activity [15, 17, 18] and normal urinary excretion of catecholamine [19], have been observed. Intravenous administration of cyclosporine in dogs causes acute reduction in relative blood flow to kidney, liver and brain [20]. The blood flow of these organs is predominantly influenced by dopaminergic activity [21]. The decreased renal blood flow might therefore be due to a reduction of dopaminergic activity. If this is the case, it can be expected that dopamine will restore the reduced renal blood flow.

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5.2 The nephrotoxic effect of cyclosporin A [CyA] can be reversed by dopamine

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Introduction

Kidney allograft survival has been improved considerably since the introduction of cyclosporine A (CyA) as compared with conventional immunosuppression [1-4]. It has been shown clinically [5, 6] and experimentally [7-11] that CyA is nephrotoxic. Soon after an infusion of CyA a reduced renal blood flow can be measured. When CyA is given for a longer period histological changes can be found as well [12]. Both effects are reversible after stopping CyA [13].

In the dog infusion of CyA for a short period resulted in significant reduction in relative blood flow to kidney, gut and brain [14]. The blood flow of these organs is predominantly influenced by dopaminergic activity [15]. The decreased renal blood flow might therefore be due to a reduction of dopaminergic activity. If this assumption is true it can be expected that dopamine will restore the reduced renal blood flow.

On the other hand, it has been suggested that sympathetic nervous system-mediated renal vasoconstriction may be responsible for the reduction in renal blood flow. In rats plasma renin activity was increased by two-fold [16]. A renal vasoconstriction may be explained by an increased sympathetic outflow or an increased vascular reactivity on a normal sympathetic outflow. Since an increased urinary excretion of catecholamine as an index of the sympathetic outflow could not be demonstrated in human heart transplant recipients [17] an increased vascular reactivity might be present. If this is the case, dobutamine which has a strong vasodilating (a beta adrenergic agonistic) and a weak vasoconstrictory (alpha adrenergic agonistic) effect, should increase vascular resistance [18] and consequently reduce renal blood flow. This increased vascular reactivity may be caused by an increased activity in renin-angiotensin-aldosterone system or a decreased activity in prostaglandin and kallikrein-kinin system. Although an increased plasma renin has been found in rats [16], inhibition of angiotensin II formation (a potent vasoconstrictor) by captopril did not prevent the CyA-induced decrease in renal blood flow. Moreover, only low plasma renin activity has been reported in CyA-treated patients [19]. It seems therefore more likely that increased vascular reactivity is not due to an increased activity of the renin-angiotensin-aldosterone system but to a decreased activity of prostaglandin and kallikrein-kinin system. Inhibition of prostaglandins synthesis with meclo-fenamate increased CyA-induced vasoconstriction. Some prostaglandins (PGE_2 and prostacyclin) have a vasodilatory activity, others such as $\text{PGF}_{2\alpha}$ and thromboxane (TxB) have a vasoconstrictory effect. A reduced renal blood flow and glomerular filtration may be expected if there is a dysbalance in this prostaglandin system.

An increased systemic vascular resistance has been reported during CyA. Dihydroergotoxine mesylate (hydergine) reduces vascular resistance by blocking alpha adrenergic receptors. Low dose of hydergine did not seem helpful in reducing CyA-induced renal toxicity and possibly higher dosage might result in a positive effect

[20]. The aim of the study is to investigate the mechanism of CyA-induced renal blood flow reduction by giving dopamine, dobutamine and hydergine. The influence of these drugs on renal hemodynamic, renin-angiotensin-aldosterone system, urinary excretion of kallikrein and prostaglandins in CyA-treated cadaveric renal transplant patients will be measured.

Patients and methods

After informed consent 3 groups of renal allograft recipients have been studied. Patients were maintained on unchanged therapeutic regimens throughout the studies. CyA dosages were adjusted to keep trough levels between 0.1 and 0.2 mg/l (whole blood, HPLC). Group A consisted of 4 women and 8 men ($n = 12$) with a mean age of 48 years (23-63 years), and a median of 10 weeks after transplantation. Dopamine 0,8 $\mu\text{g/kg BW/min}$ i.v. was given for two hours. Three to 6 days later, 7 patients received 0,8 $\mu\text{g/kg BW/min}$ dobutamine i.v. for two hours. Group B consisted of 2 women and 4 men ($n = 6$) with a mean age of 45 years (25-66 years) and a median of 6,5 weeks after transplantation. They received 1,6 $\mu\text{g/kg BW/min}$ dopamine i.v. for two hours.

Before and at the end of dopamine or dobutamine infusion, the following parameters were measured. Blood Pressure (BP) and heart rate (HR) were recorded by automatic recorder. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured by radioisotope continuous infusion method. Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were measured by radioimmunoassay. Urinary prostaglandins (PGE_2 , 6-Keto-PGF $_{1\alpha}$, metabolite of Prostacyclin. PGF $_{2\alpha}$ and TxB) were measured by radioimmunoassay, whereas urinary kallikrein was measured by enzymatic method.

Group C consisted of 1 woman and 2 men with a mean age of 46 years (38-52 years) and resp. 8, 22, 24 months after kidney transplantation without signs of chronic rejection, who were treated with hydergine resp. 6 mg daily for 4 weeks and 12 mg daily for another 4 weeks. ERPF and GFR were measured simultaneously before, after both periods.

Results

Systemic hemodynamics

There was no difference in systemic hemodynamic parameters before and after both dosages of dopamine and after dobutamine (table 1).

Table 1. Systemic hemodynamic alterations of patients in group A and group B.

A	Before		After	
				Dopamine
SAP	165 ± 7,5		167 ± 7,0	NS
DAP	101 ± 4,3		101 ± 3,6	NS
MAP	119 ± 5,0		119 ± 4,2	NS
HR	74 ± 2,6		71 ± 2,6	NS
				Dobutamine
SAP	156 ± 11,0		164 ± 12,8	NS
DAP	97 ± 8,4		98 ± 8,8	NS
MAP	114 ± 8,7		119 ± 9,2	NS
HR	70 ± 3,3		68 ± 3,0	NS
B				Dopamine
SAP	177 ± 15,7		166 ± 9,1	NS
DAP	104 ± 5,3		92 ± 1,6	NS
MAP	118 ± 7,4		110 ± 1,7	NS
HR	60 ± 5,4		59 ± 4,0	NS

Renal hemodynamics

After dopamine ERPF in group A increased significantly from $189,6 \pm 16$ to $207 \pm 19,7$ ml/min ($p < 0.005$), whereas the mean GFR did not change (resp. $39,0 \pm 4,9$ and $39,3 \pm 4,7$ ml/min). The mean ERPF of 7 patients of group A decreased significantly from $200,9 \pm 27,4$ to $190,7 \pm 24,5$ ml/min ($p < 0.05$) at the end of dobutamine i.v., whereas the mean GFR did not significantly decreased (from $41,9 \pm 7,2$ to $40,9 \pm 6,6$ ml/min). After dopamine the ERPF of patients of group B increased from $203,2 \pm 22,5$ to $273,8 \pm 36,0$ ml/min ($p < 0.005$), whereas the GFR did not change (from $45,8 \pm 3,7$ to $48,2 \pm 4,6$ ml/min). The increment of ERPF in patients of group B was higher compared to group A (resp 34 and 10%). After 4 weeks treatment with 6 mg hydergine the ERPF in patients of group C decreased from $196,3 \pm 9,7$ to $182 \pm 5,1$ ml/min and to $173 \pm 9,5$ ml/min after another 4 weeks treatment with 12 mg hydergine. The GFR decreased resp from $48,7 \pm 5,5$ via $45,3 \pm 4,2$ to $45,3 \pm 4,4$ ml/min. Since the number of patients was small, no statistical significance could be reached.

Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in group A (table 2)

The PRA was low ($0,90 \pm 0,24$, normal value: $1,67 \pm 0,83$ ngAI/ml/hour), whereas the PAC was high ($0,84 \pm 0,16$, normal value: $0,03-0,44$ mmol/l). The mean PRA did not change at the end of dopamine i.v. (from $0,90 \pm 0,24$ to $0,98 \pm 0,32$ ngAI/ml/hour) and the same was true with the mean PAC (from $0,84 \pm 0,16$ to $0,85 \pm 0,14$ mmol/l).

Figure 1.

The mean ERPF (ml/min) and GFR (ml/min) before and after 2 hours 0,8 µg/kg BW/min dopamine infusion in patients of group A (n = 12). the same parameters before and after 2 hours 1,6 µg/kg BW/min dopamine infusion in patients of group B (n = 6), and before and after 2 hours 0,8 µg/kg BW/min dobutamine infusion in patients of group A (n = 7).

*: $p < 0.05$; ***: $p < 0.005$.

Table 2.

Laboratory data before and after dopamine in patients of group A.

Group A	Dopamine		
	Before	After	Normal value
PRA	0,90 ± 0,26	0,98 ± 0,32	1,67 ± 0,83
PAC	0,84 ± 0,16	0,85 ± 0,14	0,03— 0,44
PGE ₂	5,50 ± 0,90	6,20 ± 1,50	2,50—21,00
6-Keto-PGF _{1α}	23,90 ± 4,00	31,20 ± 6,70	37,90—63,70
PGF _{2α}	10,80 ± 1,30	12,80 ± 2,00	2,10—50,30
TxB	35,10 ± 6,60	38,50 ± 6,60	10,50—22,10
Kallikrein	2,90 ± 1,10	4,00 ± 1,80	4,60 ± 74,00

Urinary prostaglandins and kallikrein in group A (table 2)

PGE₂ was normal ($5,5 \pm 0,9$, normal 2,5-20 ng/hour), and PGF_{2 α} was normal ($10,8 \pm 1,3$, normal 2,0—50,0 ng/hour) whereas 6-Keto-PGF_{1 α} was low ($23,9 \pm 4,1$, normal 37,9—63,7 ng/hour) and TxB was high ($35,2 \pm 6,6$, normal 10-22,0 ng/hour).

PGE₂ did not significantly increase after dopamine i.v. (from $5,5 \pm 0,8$ to $6,2 \pm 1,5$ ng/hour). This was also observed for PGF_{2 α} (from $10,8 \pm 1,3$ to $12,8 \pm 2,0$ ng/hour), 6-Keto-PGF_{1 α} (from $23,9 \pm 4,0$ to $31,2 \pm 6,7$ ng/hour) and TxB (from $35,1 \pm 6,6$ to $38,5 \pm 6,6$ ng/hour).

Kallikrein was low ($2,9 \pm 1,1$, normal 4,6-74 mU/hour). There was no significant difference in kallikrein before and at the end of dopamine i.v. (from $2,9 \pm 1,1$ to $4,0 \pm 1,8$ mU/hour).

Discussion

As could be expected no change of blood pressure and heart rate were observed in patients of either group A or B. The increase of ERPF must therefore be explained by intrarenal events such as shift of the blood flow to the renal cortex [21]. The higher increase of ERPF in group B compared to group A might be due to either the higher dosage of dopamine or due to the fact that patients in group B were using CyA for a shorter period.

Despite the decrease of vascular resistance by hydergine, neither dosage of hydergine resulted in an improvement of ERPF and/or GFR. Actually, a gradual decrease of ERPF was observed. It remains to be shown whether a concomittant decrease in cardiac output might be responsible for this negative effect on the ERPF.

In contrast to the low PRA in patients of group A was the high PAC that might be explained by a reduced inhibitory influence of endogenous dopamine on aldosterone secretion. A similar finding has been reported in CyA-treated heart transplant patients [17].

The low PRA in patients of group A might be explained as well by the reduced mean urinary excretion of kallikrein [22, 23]. The reduced excretion of kallikrein is a confirmation of the findings of Koolen et al [24] and might be related as well to the diminished functional tubular mass of these patients.

After infusion of dopamine there were no significant changes in PRA, PAC and urinary excretion of kallikrein. The absence of stimulation on PRA secretion is a confirmation of our earlier finding [25]. The absence of reduction of PAC might be explained by the dosage of dopamine or a reduced sensitivity of dopamine receptor on the granulosa cells of the suprarenal glands.

Excretion of PGE₂ was normal and did not increase after dopamine i.v. PGE₂ is predominantly produced in renal medulla [26, 27, 28] and a smaller portion in renal cortex [29].

Excretion of 6-Keto-PGF_{1 α} (metabolite of prostacyclin) was reduced significantly and increased almost significantly ($0.1 > p > 0.05$) after dopamine i.v. Prostacyclin is mainly synthesized in cortical arteries [30] and human glomeruli [29].

Excretion of PGF_{2 α} was normal and did not increase after dopamine i.v. PGF_{2 α} is synthesized mainly within medulla [26-28] and to a lesser extent in the cortex [29].

Excretion of TxB was significantly increased and was not increased further after dopamine. TxB is synthesized in human glomeruli [29] and it is a potent vasoconstrictor [31].

Renal prostaglandins are important for the maintenance of blood flow and glomerular filtration [32, 33]. An imbalance between vasodilatory prostaglandin and the vasoconstrictor thromboxane might play a role in renal transplant rejection [34]. This imbalance might play a role as well for the CyA induced nephrotoxicity. This imbalance is leading to an increased vascular reactivity. The existence of increased vascular reactivity is shown by the observation, that ERPF decreased after dobutamine.

In conclusion the results of our study suggests that CyA-induced decreased renal blood flow is based on imbalance between vasodilatory prostaglandins and the vasoconstrictor TxB, which may modulate renal vascular tone [35]. This imbalance may reduce dopamine activity and increase vascular reactivity. Prostaglandins influence GFR as well by directly affecting changes in mesangial contraction [31]. Since short duration of dopamine infusion does not normalise the imbalance between vasodilating and the vasoconstrictor prostaglandins, no significant changes in GFR can be expected.

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Chapter 6

Summary and conclusion

In chapter 1 a survey of the literature is given about the effects of dopamine and dopaminergic agonists on the cardiovascular system, the kidney and suprarenal glands in physiological and pathophysiological conditions.

In chapter 2 the effects of dopamine on the heart are described. After an introduction (2.1) about the pathophysiology and treatment of heart failure, two studies in patients with heart failure are described.

In 2.2 the hemodynamic and humoral effects of two doses (2,5 and 5,0 $\mu\text{g}/\text{kg}/\text{min}$) dopamine and dobutamine are compared in patients with low cardiac output following acute myocardial infarction. After infusion of the same dose of either drug the increases in cardiac output are comparable. At these doses, dobutamine has a positive chronotropic effect and increases the blood pressure. The latter is partly due to the increased plasma renin. With these dosages, dobutamine does not decrease the systemic vascular resistance. This is due to its small effect on peripheral vessels. In contrast with dobutamine, with the same dosages, dopamine has no chronotropic effect, which may be due to the stimulation of DA₂ and α_2 receptors. With these dosages dopamine does not alter plasma renin level, but it releases the endogenous noradrenaline. The unchanged blood pressure after dopamine i.v. is due to the profound reduction of systemic vascular resistance, which is partly due to the stimulation of dopamine receptors. Because of this afterload-reducing property of dopamine, preference must be given to this drug for the treatment of patients with low cardiac output following acute myocardial infarction. However, in hypotensive patients with the same clinical condition, preference must possibly be given to dobutamine.

Paragraph 2.3 deals with the treatment of refractory congestive heart failure with furosemide i.v. and low dose (0,4 and 1,0 $\mu\text{g}/\text{kg}/\text{min}$) of dopamine i.v. These doses of dopamine cause afterload reductions by particularly reducing the renal vascular resistance. With these doses, dopamine in combination with furosemide is more effective than furosemide alone in promoting the excretion of salt and water excess whereas renal function is preserved.

In chapter 3 the effects of dopamine on peripheral vasculature are described.

In the introduction (3.1) the potential mechanisms of essential hypertension are described. Reduced renal dopamine activity which leads to reduced sodium excretion might be one of the mechanisms. This may increase the resting tone in vascular smooth muscle cells and the vascular response to adrenergic stimuli. Two studies are

described which may lend some support to this hypothesis.

In 3.2 the hemodynamic and humoral effects of dopamine in two groups of patients were studied. The first group consisted of hypertensive patients, whose blood pressure returned to normal after acute myocardial infarction. The second group consisted of normotensive patients whose blood pressure remained normal after acute myocardial infarction. After 2,5 and 5,0 $\mu\text{g}/\text{kg}/\text{min}$ dopamine i.v. the increases in cardiac output in both groups are comparable. In previously hypertensive patients the blood pressure increases significantly without alteration in the systemic vascular resistance. In contrast, the previously normotensive group shows unchanged blood pressure with a significant reduction in systemic vascular resistance. The different hemodynamic responses to dopamine in previously hypertensive patients may be based on the vascular hyporeactivity to the dopaminergic receptor-stimulating property of this drug. A vascular hyperreactivity to noradrenaline may also play a role.

In 3.3 the hemodynamic and humoral effect of dobutamine in the same two groups of patients of 3.2 were studied. After 2,5 and 5,0 $\mu\text{g}/\text{kg}/\text{min}$ dobutamine i.v. the increases in cardiac output in both groups are comparable. In the previously hypertensive group the mean blood pressure and systemic vascular resistance increase. In the previously normotensive group the mean blood pressure does not change significantly and systemic vascular resistance decreases. This suggests a vascular hyperresponsiveness to the alpha-adrenergic receptor-stimulating property of dobutamine in hypertensive patients whose blood pressure returned to normal after acute myocardial infarction.

The results of these two studies suggest that hypertensive patients might have a dopaminergic vascular hyporesponsiveness and an alpha-adrenergic vascular hyperreactivity.

In chapter 4 the influence of dopamine on the adrenal gland is described. Endogenous dopamine has a tonic inhibitory effect on aldosterone secretion. The effects of endogenous dopamine can be inhibited by the dopamine antagonist, metoclopramide, resulting in an increase of aldosterone secretion. In patients with primary hyperaldosteronism conflicting results of the response of plasma aldosterone to metoclopramide have been reported. Different plasma levels of potassium might explain the discrepancy in the various studies. In 4.2 the effect of metoclopramide on aldosterone secretion in essential hypertensives and patients with primary hyperaldosteronism are compared. Both groups have normal plasma potassium levels when treated with amiloride. In patients with primary hyperaldosteronism the relative increases in plasma aldosterone concentration after metoclopramide i.v. are significantly smaller than that in essential hypertensives. This finding indicates that metoclopramide can be used as a screening test in hypertensive patients for the detection of primary hyperaldosteronism.

In chapter 5 the effects of dopamine on the kidney are described. Cyclosporine nephrotoxicity has been shown in heart-, liver-, bone-marrow- and kidney trans-

plantation. The mechanism, causing this nephrotoxicity, is still unknown. In patients using cyclosporine reduced renal plasma flow and glomerular filtration rate, increased renal vascular resistance, low plasma renin activity and normal urinary excretion of catecholamine have been reported. From a study in dogs, the hypothesis is formulated that cyclosporine nephrotoxicity is partly caused by depressing the dopaminergic activity. In 5.2 indirect evidence is delivered in favour for this hypothesis when after 0,8 and 1,6 $\mu\text{g/kg/min}$ dopamine i.v. renal plasma flow increased significantly in renal allograft recipients, who received cyclosporine. However, comparative studies on the effects of calcium entry blockers and dopamine on the nephrotoxicity of cyclosporin in renal allograft recipients have not been carried out.

Our study shows that the effects of dopamine i.v. in hypertensives differ from those in normotensive subjects. This may suggest a role for endogenous dopamine in the pathogenesis of hypertension. The reduced or increased activity of endogenous dopamine can even be the cause of some disorders. Exogenous dopamine has beneficial clinical effects on various organs, provided that the optimal dose is given based on the correct indication.

Samenvatting en conclusies

Hoofdstuk 1 bevat een literatuurstudie over de effecten van dopamine en dopaminerge agonisten op het hart- en vaatstelsel, de nieren en bijnieren in fysiologische en pathofysiologische omstandigheden.

In hoofdstuk 2 zijn de effecten van dopamine op het hart beschreven. Nadat de pathofysiologie en de behandeling van hartinsufficiëntie zijn behandeld (2.1), zijn twee onderzoeken bij patiënten met hartinsufficiëntie beschreven.

De hemodynamische en humorale effecten van twee doseringen (2.5 en 5.0 $\mu\text{g/kg/min}$) dopamine en dobutamine zijn vergeleken bij patiënten met laag hartminuutvolume ten gevolge van een acuut myocardinfarct (2.2). Tijdens de intraveneuze toediening van elk van beide geneesmiddelen in dezelfde dosering zijn de stijgingen in het hartminuutvolume vergelijkbaar. In deze doseringen heeft dobutamine een verhogend effect op de hartfrequentie en de bloeddruk en geen verlagend effect op de vaatweerstand.

Een verhoogd plasma renine veroorzaakt onder andere deze bloeddrukstijging, terwijl de geringe invloed van dobutamine op de perifere vaten de onveranderde vaatweerstand verklaart. In tegenstelling tot dobutamine heeft dopamine in dezelfde doseringen geen invloed op de hartfrequentie en het plasma renine. De stimulatie van DA₂ en α -2 receptoren zou een verklaring van de afwezigheid van een chronotroop effect kunnen zijn. De onveranderde bloeddruk tijdens de intraveneuze toediening van dopamine berust op een grote daling van de vaatweerstand. Deze daling van de vaatweerstand berust op de stimulatie van de dopaminereceptoren. Vanwege de eigenschap van dopamine om de afterload te verlagen, verdient dopamine de voorkeur boven dobutamine bij de behandeling van patiënten met een laag hartminuutvolume op basis van het acute myocardinfarct. Indien deze patiënten een hypotensie hebben, verdient dobutamine de voorkeur boven dopamine.

De behandeling van refractaire congestieve hartinsufficiëntie met intraveneuze toediening van furosemide en lage dosering dopamine (0.8 $\mu\text{g/kg/min}$) is in paragraaf 2.3 beschreven. Bij deze dosering bewerkstelligt dopamine een daling van de afterload, verder wordt niervaatweerstand verlaagd. Bij deze dosering is dopamine in combinatie met furosemide werkzamer dan furosemide alleen in het verwijderen van overtollige zout en water, terwijl de nierfunctie niet wordt benadeeld.

In hoofdstuk 3 zijn de effecten van dopamine op het perifere vaatstelsel beschreven. De potentiële pathofysiologische mechanismen, die tot essentiële hypertensie kunnen leiden, zijn in de introductie (3.1) aangegeven. Een verlaagde dopamine-activiteit in de nier, die tot een verminderde zoutuitscheiding leidt, zou een van die

mechanismen kunnen zijn. Dit zou de basale tonus van de vaatspiercellen en de vaatreactie op adrenergische prikkels doen verhogen. Twee onderzoeken zijn beschreven, die deze hypothese zouden kunnen ondersteunen. De hemodynamische en humorale effecten van dopamine zijn bij twee groepen patiënten bestudeerd (3.2). De eerste groep bevatte patiënten met hypertensie, waarbij de bloeddruk normaliseerde na het acute myocardinfarct. De tweede groep bevatte patiënten met een normale bloeddruk, waarbij de bloeddruk normaal bleef na het acute myocardinfarct. Tijdens de intraveneuze toediening van 2.5 en 5.0 $\mu\text{g/kg/min}$ dopamine zijn de stijgingen van het hartminuutvolume van beide groepen vergelijkbaar. Bij de patiënten, die voorheen hypertensie hadden, stijgt de bloeddruk zonder enige verandering in de vaatweerstand. Daarentegen blijft bij patiënten, die voorheen een normale bloeddruk hadden, deze bloeddruk onveranderd, terwijl een daling van de vaatweerstand optreedt. Deze verschillen zouden op een vasculaire hyporeactiviteit op de dopaminerge receptor stimulerende eigenschap van dopamine kunnen wijzen bij patiënten met hypertensie. Ook zou een vasculaire hyperreactiviteit op noradrenaline een rol kunnen spelen. De hemodynamische en humorale effecten van dobutamine zijn bij dezelfde groepen patiënten van 3.2 bestudeerd (3,3). Tijdens de intraveneuze toediening van 2.5 en 5.0 $\mu\text{g/kg/min}$ dobutamine zijn de stijgingen van het hartminuutvolume van beide groepen vergelijkbaar. Bij de patiënten, die voorheen hypertensie hadden, stijgen de bloeddruk en de vaatweerstand. Bij de patiënten, die voorheen een normale bloeddruk hadden, blijft de bloeddruk onveranderd en daalt de vaatweerstand. Dit suggereert een vasculaire hyperreactiviteit op de alfa-adrenerge receptor stimulerende eigenschap van dobutamine bij de voorheen hypertensieve patiënten.

De resultaten van deze twee studies suggereren, dat hypertensieve patiënten een dopaminerge vasculaire hyporeactiviteit en een alfa-adrenerge vasculaire hyperreactiviteit zouden kunnen hebben.

In hoofdstuk 4 is de invloed van dopamine op de bijnieren beschreven. Endogene dopamine heeft een tonisch remmend effect op de secretie van aldosteron. Deze effecten van endogeen dopamine kunnen door de dopamine-antagonist, metoclopramide, voorkomen worden met als gevolg een stijging van de aldosteronsecretie. Tegenstrijdige resultaten over de veranderingen van plasma aldosteron ten gevolge van metoclopramide bij patiënten met primair hyperaldosteronisme zijn gerapporteerd. Verschil in plasmaspiegels van kalium zou de tegenstrijdigheid van de verschillende studies kunnen verklaren. De effecten van metoclopramide op de aldosteronsecretie bij patiënten met essentiële hypertensie en patiënten met primair hyperaldosteronisme zijn vergeleken (4.2). Beide groepen hadden een normaal plasma kaliumspiegel ten gevolge van voorbehandeling met amiloride.

De relatieve stijging van plasma aldosteron concentratie na de intraveneuze toediening van metoclopramide is beduidend lager bij patiënten met primair hyperaldosteronisme dan bij patiënten met essentiële hypertensie. Deze bevinding geeft aan dat

toediening van metoclopramide gebruikt kan worden als een screening test bij hypertensiepatiënten voor het opsporen van primair hyperaldosteronisme.

In hoofdstuk 5 worden de effecten van dopamine op de nieren beschreven. Ciclosporinenefrotoxiciteit is in hart-, lever-, beenmerg- en niertransplantatie aangetoond. Het mechanisme van de nefrotoxiciteit is nog onbekend. Verlaagde nierdoorstroming en glomerulaire filtratiesnelheid, verhoogde niervaatweerstand, lage plasma renine-activiteit en normale uitscheiding van catecholamine in de urine zijn waargenomen bij patiënten, die ciclosporine gebruiken. Op basis van de gegevens uit een onderzoek bij honden is een hypothese geformuleerd, dat ciclosporinenefrotoxiciteit deels is veroorzaakt door een verlaging van de dopaminerge activiteit. Een indirect bewijs is geleverd ter ondersteuning van deze hypothese (5.2). Tijdens de intraveneuze toediening van 0.8 en 1.6 $\mu\text{g/kg/min}$ dopamine neemt de nierdoorstroming van de met ciclosporine behandelde niertransplantatiepatiënten toe. Vergelijkende studies over de effecten van calciumantagonisten en dopamine op de nefrotoxiciteit van ciclosporine zijn tot dusver niet bekend.

Onze studie laat zien, dat de effecten van intraveneuze toediening van dopamine bij essentiële hypertensie patiënten anders zijn dan dat bij normotensieve patiënten. Dit suggereert dat endogene dopamine een rol kan spelen in de pathogenese van hypertensie. De verlaagde of verhoogde activiteit van endogene dopamine kan zelfs de oorzaak van sommige aandoeningen zijn. Exogene dopamine heeft klinisch gunstige effecten op verschillende organen, mits de optimale dosering op de juiste indicatie wordt gegeven.

Nawoord

Velen wil ik danken voor hun hulp bij het verschijnen van dit proefschrift, waarbij ik mij terdege realiseer dat dit nooit tot stand gekomen zou zijn zonder de bereidwillige medewerking van de patienten die aan het onderzoek hebben deelgenomen.

In de eerste plaats wil ik mijn promotor, Prof.Dr. J.A. Flendrig, bedanken. Beste Guus, dankzij jouw stimulerende adviezen en kritische begeleiding is dit proefschrift tot stand gekomen. Dat je ondanks je drukke bestaan altijd aandacht en tijd voor me had, heb ik zeer gewaardeerd.

Ook mijn co-promotor, Dr. J.P. van Hooff, wil ik bedanken voor zijn talrijke adviezen waardoor het onderzoek mede in goede banen is geleid.

Prof.Dr. W.H. Birkenhäger, mijn dank gaat vooral uit voor de opleiding, die ik bij u heb genoten. Zeer veel waardering heb ik voor uw deskundigheid op het gebied van hypertensie.

Dr. P.J. Lijnen, dankzij jouw inspanning zijn de vele monsters, zowel plasma als urine, op betrouwbare wijze bewerkt.

Dr. G.J.J. Teule, Dr. G. Heidendal en medewerkers van het isotopenlaboratorium, jullie dank ik voor de hulp bij de metingen van de nierdoorstroming en de glomerulaire filtratiesnelheid.

De referenten Prof.Dr. A. Amery, Prof.Dr. M.A.D.H. Schalekamp en Prof.Dr. H.J.J. Wellens ben ik zeer erkentelijk voor de bereidwilligheid, waarmee ze het uiteindelijke werk hebben beoordeeld.

Collega Leunissen, mijn hartelijke dank voor je opbouwende kritiek en samenwerking.

Alle collegae van zowel de afdeling Interne Geneeskunde als de afdeling Cardiologie, de verpleegkundigen van de afdeling Nier- en Pancreastransplantatie, Cardiologie en van het Dagcentrum dank ik voor hun medewerking bij het verrichten van het onderzoek.

Anke Hendriks-Wijnands en Desirée van Schoubroeck, mijn dank gaat speciaal naar jullie uit vanwege de vele uren, die jullie met groot incasseringsvermogen en toewijding aan het uittypen en corrigeren van dit proefschrift hebben besteed.

Paul Brouwers en Bert Schutte hebben vele uren doorgebracht achter het beeld-

scherm van de computer om het manuscript zodanig te bewerken, dat het naar de drukkerij kon. Nogmaals mijn dank hiervoor.

Tenslotte wil ik mijn vrouw Imelda en onze dochter Marcia van harte danken voor hun geduld en de gegeven steun.

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