The prophylactic use of low dose dopamine for the prevention of radio opaque contrast media induced acute renal failure in diabetic patients with pre-existing renal impairment undergoing trans femoral angiography.

A comparison between the currently used dose with a lower dose of dopamine.

An MSc Thesis

By

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3. Abstract

3.1. Background

It has long been recognised that diabetes causes complications. Microvascular problems include an increase in the incidence of retinopathy and neuropathy. Macrovascular complications lead to the increased incidence of cardiovascular morbidity and mortality seen in these patients.

Nephropathy is a microvascular complication and renal function is known to transiently worsen with contrast media. Contrast media is used in the assessment in a macrovascular complication - that of lower limb peripheral vascular disease.

It has previously been shown that pre existing renal impairment can worsen with the administration of intravenous radio opaque contrast media. To help prevent this complication dopamine has been used as a continuous intravenous infusion. The optimal dose to use for this indication is not known.

3.2. Methods

This study was designed to compare 2 doses - the currently used 2.5 μg.kg^{-1}.min^{-1} and a lower dose - 1 μg.kg^{-1}.min^{-1} and assess the renal protective effect of both.

36 consecutive patients were enrolled in the study. Of these 17 were controls. They had normal pre angiogram renal function i.e. serum creatinine < 100 μmol/l. The remaining patients had abnormal renal function i.e. serum creatinine >100 μmol/l but <182 μmol/l. Of the second group, 10 patients had the currently used dose of dopamine and 9 patients had the lower dose. Serum creatinine was measured pre angiogram and then at 24 and 48 hours post angiogram.

3.3. Results

These show that the control group had no significant change in serum creatinine with the administration of contrast media.

The group having 2.5 $\mu g.kg^{-1}.min^{-1}$ had a statistically significant improvement in serum creatinine at 24 hours ($p = 0.009$) but at 48 hours this benefit had been lost and the creatinine was comparable to the control group ($p = 0.163$).

The group receiving 1 $\mu g.kg^{-1}.min^{-1}$ had no significant change in serum creatinine at either 24 or 48 hours compared with the control group ($p = 0.140$).

3.4. Conclusions

These results show that whilst there is a modest - but significant - improvement in renal function with the higher dopamine dosage this is not sustained over 48 hours. The lower dose, whilst not improving the serum creatinine, does not allow any deterioration in renal function with this investigation.

The use of 1 $\mu g.kg^{-1}.min^{-1}$ of dopamine as an infusion for 1 hour prior and 6 hours post trans femoral angiography in well hydrated patients with pre angiogram serum creatinine levels between 100 μmol/l and 182 μmol/l is advocated as prophylaxis against the development of Radio Opaque Contrast Induced Nephropathy (ROCIN).

4. Abbreviations

ROCIN	Radio opaque contrast-media induced nephropathy
GFR	Glomerular filtration rate
ERBF	Effective renal blood flow
ERPF	Effective renal plasma flow
DA	Dopamine (receptors)

5. Introduction

Long standing, poorly controlled diabetes mellitus can be associated with a number of complications. These include both macro and micro vascular problems. Of these, the nephropathy leads to the commonest cause of end stage renal failure in the developed world[(1)].

Peripheral vascular disease also is a major problem. Part of the investigation of the severity of the vasculopathy includes trans femoral angiography.

It is well recognised that radio opaque contrast media can precipitate acute renal failure, most frequently in those patients with previously impaired renal function [(2)].

Various studies have explored the possibility of finding a method to protect the kidneys against this adverse effect in a necessary investigation. One of these methods has been found to be the prophylactic infusion of 'renal dose' dopamine. However, there has been controversy as to firstly, whether this drug works at all, and secondly, as no formal studies have been carried out - what the 'optimal' dose of dopamine for this procedure is.

5.1. The pharmacology of dopamine

Dopamine (DA) (3, 4 dihydrophenylethylamine) is an endogenous catacholamine first synthesised in 1910 [3]. When infused intravenously it reaches a steady state in 5 - 30 minutes. It exerts a bi phasic effect on blood pressure depending on the receptor that is activated. It acts on DA receptors - both DA_1 and DA_2 - and both α and β adrenoceptors. At low doses it works predominantly on the DA_1 receptor, with decreasing effect on the DA_2, α_2, α_1 and β_1. It has negligible effect on the β_2 receptor at low dose.

DA_1 receptors are post synaptic and are widely distributed in smooth muscle cells. They are vasodilatory. Both DA_1 and DA_2 receptors are widely distributed in the kidney. Whether they are evenly dispersed or, as is more likely, selectively distributed, is unknown.

DA_2 are presynaptic and act as α_2 adrenoceptor agonists - by preventing the re-uptake of noradrenaline by the presynaptic membrane and so prolonging the vasoconstrictor effect of the noradrenaline.

At higher doses of 5 - 10 $\mu g.kg^{-1}.min^{-1}$, dopamine is both an α and β adrenergic receptor agonist and causes vasoconstriction. In early studies using dopamine the doses used were so high that no vasodilatory effect was seen, only marked renal and systemic vasoconstriction. This led to the initial feeling that dopamine was predominantly a pressor agent acting on the a adrenoceptors (4). However with further study the low dose, vasodilator effect was eventually elucidated (5).

Stimulation of DA receptors and their effect on renal haemodynamics can be measured using renal vascular resistance and glomerular filtration rate (GFR), and effective renal blood flow (ERBF). It was shown some time ago that low dose infusions can increase ERPF, GFR and urinary sodium excretion (by inhibiting proximal tubular sodium reabsorbtion in euvolaemic patients). This was in clear contrast to other catacholamines available at the time [6, 7].

There is a dose response curve to the actions of dopamine (Figure 1). The first receptors to be activated are the DA_1 and DA_2 at a range of 0 - 100% at 0.5 - 5 $\mu g.kg^{-1}.min^{-1}$, with the β and α being activated at 2 and 5 $\mu g.kg^{-1}.min^{-1}$ respectively and being 100% activated at 30 $\mu g.kg^{-1}.min^{-1}$ [8, 9]. There is clearly an overlap between receptor binding affinities, and so, effect. It is difficult to tell whether an effect is dopaminergic, α adrenergic or a β adrenergic effect at e.g. 3 - 5 $\mu g.kg^{-1}.min^{-1}$. It is possibly a combination.

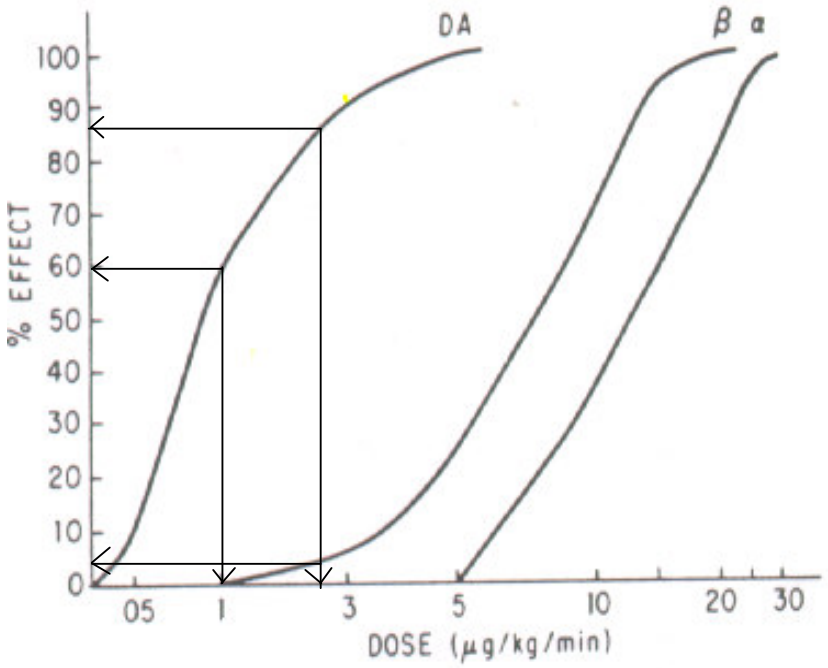


Figure 1

Dopamine related effects in man. At low doses (≤ 3 mg.kg^{-1}.min^{-1}), pharmacological effects are limited to those resulting from stimulation of DA receptors. With increasing doses, stimulation of b and a adrenoceptors is observed. Modified from reference 9. Reproduced with kind permission of the publishers. © Swets & Zeitlinger Publishers.

Doses < 5 $\mu g.kg^{-1}.min^{-1}$ may be described as 'subpressor' doses, i.e. they do not usually increase blood pressure. However, if at the lower doses there is a reduction in the DA receptor activation then this may lead to a reduction in the increase in renal blood flow. The alternative explanation for this is that at the higher doses where β adrenoceptor activation (i.e. the positive inotropic and chronotropic effects on the heart) is also taking place, then the opposing action of the DA and the β receptors may counteract each other. By using the lower dopamine dose, and so avoiding β activation, the overall renal blood flow may be unchanged. The effect of the β activation using the higher doses can be proven by abolishing it by using selective β adrenoceptor blockade (10).

6. Aim

This study was designed to find whether a lower dose of dopamine than is currently used can safely prevent ROCIN in diabetic patients undergoing lower limb angiography. This was hoped to lead to a change in clinical practice where the drug was given at this lower dose rather than the dose used at present. This would lead - amongst other things - to a potentially substantial saving in drug costs.

At present this drug is being infused into a large peripheral vein. If the Summary of Product Characteristics is to be followed, then it should be given through a central venous line as it is highly irritant in either high doses or when given in a concentrated solution. If it can be shown that the lower dose of the drug is as efficacious as the higher dose then the drug would be potentially safer to give. The risk of tissue damage due to extravasion would be reduced.

7. Null Hypothesis

That the particular dose of dopamine under study is no different from the currently used dose in the prevention of radio opaque contrast media induced acute renal failure.

8. Methods and Patients

Setting - Kings College Hospital, a London teaching hospital.

Patients - Those admitted with evidence of peripheral vascular disease, diabetes mellitus and, after clinical and vascular laboratory assessment, the need for angiography / angioplasty by the interventional radiologists.

Methods - 36 Patients fell into one of the following three groups

1) 10 diabetic patients with a serum creatinine > 100 μmol/l and < 182 μmol/l on dopamine infusion of 2.5 $\mu g.kg^{-1}.min^{-1}$.
2) 9 diabetic patients with a serum creatinine > 100 μmol/l and < 182 μmol/l on dopamine infusion of 1 $\mu g.kg^{-1}.min^{-1}$.
3) 17 diabetic patients with a serum creatinine < 100 μmol/l undergoing angiography in whom prophylactic dopamine was not required. This was the control group.

A study protocol was written and assessed by the study supervisors. After initial agreement it was also assessed by consultants within the renal and radiology departments. Once this had been obtained, a submission was made to the Ethics Committee for their approval. Eventually this was given and the study went ahead.

The study lasted between February and May 1999. 43 Consecutively admitted patients to the diabetic unit in need of vascular assessment were asked to participate. Of these, 1 fell outside of the inclusion criteria and so was not included - his results are seen in the appendix. One patient refused to go on the test dose and so was included in the standard dose group and one patient refused to have the angiogram altogether. 3 patients had abnormal renal function prior to angiography but did not have the prophylactic dose of dopamine at either dose, (of these one had diabetes diagnosed 1 month prior to admission). This was due to clinical error. Their results can also be seen in the appendix.

All of the patients had their serum creatinine measured at the appropriate times, but 17 did not have a complete set of renal measurements made, usually the urea being omitted. This is because at our institution urea is not normally part of the standard 'renal' tests unless specifically asked for. Statistical analysis was therefore not performed on this parameter.

Patients were well hydrated by having physiological (0.9%) saline infused intravenously at 100 mls/hr for at least 2 hours prior to the procedure. During the procedure the patients were injected with between 80 - 200 millilitres of *Visipaque* (Nycomed - Birmingham, UK), a low molecular weight, non ionic contrast medium. Volumes of contrast given to patients varied depending on patient weight and was also operator dependant. Patients had their serum urea and creatinine levels checked prior to the procedure and at 24 and 48 hours post procedure. The results were recorded (see appendix).

8.1. Why these levels of serum creatinine?

A rise in serum creatinine of > 27 μmol/l (0.3 mg/dl) above basal creatinine *and* a rise of > 20% above baseline would constitute a significant deterioration in renal function. (These figures have been chosen as different authors have given various ranges for their definition and these are the lowest thresholds quoted. Range 27 - 90 μmol/l, 0.3 - 1 mg/dl) [11, 12].

8.2. Present practice and explanation of levels of serum creatinine chosen.

The level of 100 μmol/l of creatinine (1.1 mg/dl) as a cut off for the administration of dopamine was chosen as this is the current threshold used in our hospital. The upper limit of 182 μmol/l (2.0 mg/dl) was chosen as this is well within the highest creatinine used as entry criteria for patients entering previous studies (255 μmol/l, 2.8mg/dl). In those studies it has been shown that even in patients with these higher levels, any deterioration in renal function was reversible back to baseline within 7 days [13].

8.3. Why serum creatinine measurement?

Serum creatinine is an insensitive measurement in patients with normal kidneys as more than a 50% reduction in GFR may occur without any significant rise. However it is an accurate test in patients with renal impairment to assess any further deterioration in renal function after the administration of contrast media. Neither 2 hour nor 24 hour creatinine clearances were used as they are not good markers for measuring GFR as creatinine is secreted by both the glomeruli and the tubules and may lead to an underestimation of the GFR.

Urinary enzyme excretion bears no relationship between the degree of reduction in GFR and the amount of enzymuria and so is not a useful marker of functional deterioration - indeed, it is a normal finding to see a peak 6 hours post contrast in the excretion of a variety of enzymes, e.g. brush boarder enzymes, lysosomal enzymes and cytosol enzymes.

8.4. Why this number of patients in each group?

10 patients per group were needed to achieve 80% power at the 5% significance level. This was to detect a difference in the mean change in serum creatinine of - 45 μmol/l in one group vs. - 9 μmol/l in the other (i.e. improvements in the serum creatinine in both the group receiving 2.5 $\mu g.kg^{-1}.min^{-1}$ and the group receiving 1$\mu g.kg^{-1}.min^{-1}$) assuming a standard deviation in each group of 27 μmol/l. This difference is well within the difference found previously between groups receiving and not receiving dopamine [14].

8.5. Exclusion criteria

Those with initial renal impairment with a serum creatinine >182 μmol/l. Those with previously known sensitivity to radio opaque contrast media. Those with shell fish allergy. Those people in whom dopamine was contra indicated - previously documented or currently present atrial or ventricular tachyarrhythmias or a history of phaeochromocytoma. Those patients on potentially nephrotoxic drugs, e.g. vancomycin, non steroidal anti inflammatory drugs, gentamicin, etc..

9. Results

In the study group receiving the test dose of 1 μg.kg^{-1}.min^{-1} one patient had a rise in serum creatinine of 27 μmol/l which represented a 21% rise in creatinine when compared with baseline (i.e. pre contrast creatinine).This did not reach the criteria which had been set out at the onset as our definition of 'renal failure'. This was a rise in serum creatinine of *greater* than 27 μmol/l *and* a rise of 20% above baseline. This patient did not develop any evidence of acute renal failure sufficient to merit further medical intervention. The subsequent blood test done 4 days later showed a creatinine of less than that prior to the procedure.

In the group treated with the standard dose of 2.5 μg.kg^{-1}.min^{-1} of dopamine only one of the patients had an increase of their serum creatinine above the >27 μmol/l and a 20% rise in creatinine above baseline. This patient had a rise of 31 μmol/l which represented a rise above baseline of 25.4%.

The serum creatinine appeared to be rising, however no further blood tests were done until 9 days later during which time they had not developed any evidence of acute renal failure sufficient to merit further medical intervention. A blood test done at 11 days post angiogram showed a creatinine which was lower than the pre angiogram measurement.

Within the control group no patients had a significant deterioration in renal function, however, 1 patient developed an unrelated cardiovascular complication - a myocardial infarction - some 2 weeks post angiogram. Their renal function only deteriorated with the development of cardiogenic shock complicated by ischaemic hepatitis and hepato-renal syndrome. The patient did not do well and eventually died 29 days post angiogram.

The 1 patient who had both an angiogram and then an angioplasty with an initial creatinine >182 μmol/l subsequently did not have a significant rise. On both occasions, as he fell outside of the inclusion criteria, he was given dopamine at 2.5 $\mu g.kg^{-1}.min^{-1}$. This is a single observation and no inferences can be drawn from it.

10. Statistical analysis

Done using the SSPS system.

Table 1

Percentage increase in creatinine above baseline :-

	24 Hours	48 Hours
	Mean (Standard Error)	Mean (Standard Error)
Control Group	3.9% (1.2%)	4.1% (1.9%)
2.5 $\mu g.kg^{-1}.min^{-1}$	-7.7% (3.2%)	-0.9% (5.6%)
1 $\mu g.kg^{-1}.min^{-1}$	4.0% (4.7%)	10.2% (4.0%)
Significance	p = 0.009	p = 0.163

Repeated measures analysis of variance.

The dependant variable = percentage increase in creatinine.

The between - subjects factor = study group.

The within subjects factor = time (24 or 48 hours).

Interaction between group and time :
F = 2.09; degrees of freedom = 2, 33;

p = 0.140 i.e. not significant.

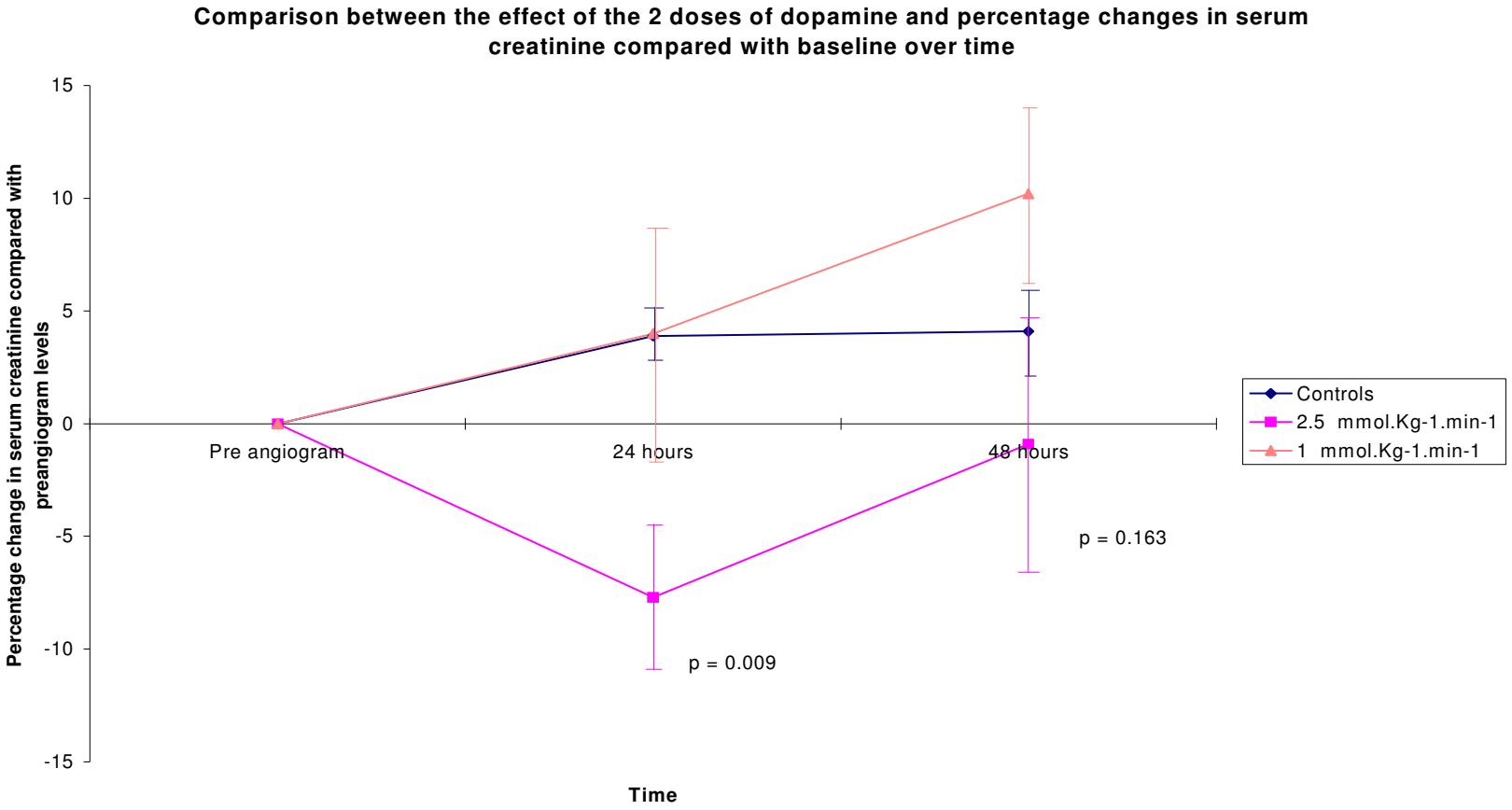
Main effect of group:
F = 23.09; degrees of freedom = 2,33;

p = <0.0005 i.e. significant

Main effect of time:
F = 10.80; degrees of freedom = 1,33;

p = 0.002 i.e. significant.

These figures show that there is a difference between the two doses at 24 hours, with a highly statistical reduction in serum creatinine at 24 hours in the 2.5 $\mu g.kg^{-1}.min^{-1}$ group. At 24 hours there is no difference in change in serum creatinine in the 1 $\mu g.kg^{-1}.min^{-1}$ compared with the control group. However, this difference is abolished by 48 hours with neither groups being significant when compared with the control group.


Comparison between the effect of the 2 doses of dopamine and percentage changes in serum creatinine compared with baseline over time
Percentage change in serum creatinine compared with preangiogram levels
15
10
5
0
-5
-10
-15
Pre angiogram
24 hours
48 hours
Time
p = 0.009
p = 0.163
Controls
2.5 mmol.Kg-1.min-1
1 mmol.Kg-1.min-1

11. Discussion

One of the most widely accepted definitions of ROCIN is “An acute impairment of renal function that follows exposure to radiographic contrast materials and for which alternative aetiologies for the renal impairment have been excluded” (15, 16).

Rates of ROCIN vary from 0 - 0.5 % in a random population without pre existing renal disease to 100 % in people with both diabetes and previous renal impairment, the incidences rising proportionally with the degree of initial renal impairment. In patients with serum creatinine of between 135 to 410 μmol/l the rate of ROCIN is 50% in the diabetic population compared with only 3% in the non diabetic population with the same serum levels (15, 16). (Usually) short term renal replacement therapy (i.e. dialysis) is necessary in up to 15% of cases (17).

This deterioration is thought to be due to a combination of factors, including contrast induced renal vasoconstriction (and so an increase in renal vascular resistance and a corresponding reduction in renal blood flow (RBF)), ischaemia, direct tubular toxicity and intra tubular obstruction by casts. The vasoconstriction may be due to selective inhibition of the vasodilatory prostaglandin phase, upsetting the physiological balance of renal blood flow. The acute changes may resolve within hours followed by a decline in renal function which may last for several days. These changes may be divided into the tubular effects and the haemodynamic effects.

Vasoconstriction causes a decrease in RBF and GFR leading to a fall in filtration pressure and so retention of normally filtered blood products. In non renal tissues a time of vasoconstriction is usually followed by a prolonged period of reactive hyperaemia. Not so in the renal beds, the opposite is found, with initial vasodilation and then a prolonged vasoconstriction (18). A study done on canine renal beds using 5 hydroxytryptamine, noradrenaline and contrast

media found that the vasoconstrictor effects of the first 2 compounds were

blocked completely by the α and β blocking agent, phenoxybenzamine. However the contrast media induced vasoconstriction was only abolished after the build up of tachyphylaxis of angiotensin.

Tubular effects may be functional or structural.

The functional effects are due to the contrast medium interfering with water and sodium reabsorbtion and so precipitating a diuresis and naturesis which may alter both tubular regulatory mechanisms and intratubular pressures [19]. This naturesis and diuresis can activate the tubuloglomerular feedback mechanism which is mediated by chemicals such as adenosine and angiotensin II. These lead to a constriction of afferent glomerular arterioles so leading to a decrease in GFR and an increase in renal vascular resistance. This mechanism may account for up to 50% of the changes in renal vascular resistance in ROCIN [19].

Structural effects may result from the internalisation of contrast from the tubules causing lysosomal changes. These are reversible and do not seem to harm the cell, the low osmolar contrast media being taken up more effectively than the high osmolar contrast [20].

Tubular injury also involves an increase in cell membrane permeability with a corresponding decrease in cell integrity leading to a leak into the intestitial fluid and a mechanical obstruction of urinary flow. Further obstruction can occur due to precipitation of contrast within the tubular lumen (in vitro urates, oxalates, Tamm Horsfall protein and abnormal protein co-precipitate with the contrast but do not usually cause obstruction in vivo) [2].

Within the renal medulla the production of the naturesis requires an high metabolic requirement for active transport to take place. This requires oxygen and this in turn makes the region susceptible

to ischaemia [21]. One of the mechanisms that frusemide may help prevent the development of ROCIN is by inhibiting the uptake of

sodium and so reducing metabolic demand, so reducing the amount of oxygen required and so reducing hypoxia [22].. Also within these regions are found areas of DNA fragmentation which are associated with an increased incidence of apoptosis. This could play an important role in nephron injury and subsequently ROCIN [23].

Recently, a novel peptide called endothelin was found within the endothelium, the epithelial and glomerular mesangial cells. This has a very similar effect on the renal beds as does contrast media. It is a very powerful vasoconstrictor and causes a decrease in GFR associated with a naturesis and diuresis by reducing proximal tubular sodium reabsorbtion. It was found that contrast media stimulated the release of endothelin [24]. In those patients in whom the endothelin concentration was greatest following contrast administration, they also had the most significant deterioration in

renal function. This leads to the hypothesis that endothelin may play a role in the pathophysiology of ROCIN [25].

Any combination of these factors may contribute to the development of ROCIN.

Several studies have shown that there are a number of predisposing factors to the development of ROCIN. The most consistent factors seem to be the presence of a combination of pre existing renal impairment and diabetes mellitus. Diabetics with normal renal function are usually at no additional risk providing they have no other co existing morbidity as is shown by the control group in this study. If it does occur then most cases resolve within 3-4 days, with cases requiring long standing renal replacement therapy fortunately being rare.

Other conditions also predispose to the development of ROCIN, but these are of lesser importance. These include dehydration, bi ventricular cardiac failure [26], high osmolar contrast [11], large

volumes of contrast and concomitant administration of other potentially nephrotoxic drugs, e.g. NSAID's and aminoglycosides (2).

Intravenous contrast is less damaging than intra arterial administration (17).

Previous studies have shown that the use of renal dose dopamine - a sympathomimetic vasodilating agent - can help to prevent this potentially disastrous complication. However the optimal dose is not known.

Diabetes is known to lead to glomerular hyperfiltration, renal hyperperfusion and so lead to nephromegaly. The mechanisms for this are still under investigation (27).

Different studies for the prevention of ROCIN have used different doses of dopamine ranging from 2 - 5 $\mu g.kg^{-1}.min^{-1}$ (28 - 30). Of these, the studies by Kapoor et al and Hans et al have been shown to

increase ERPF and either prevent deterioration in renal function or even improve it - as measured by creatinine clearance (despite this being an inaccurate measure of renal function). The study by

Weisberg et al showed no benefit in the use of dopamine against other methods of renal protection using mannitol and frusemide. A more recent study in healthy volunteers confirmed that effective renal plasma flow (Figure 3) but not GFR (Figure 4) increases with an infusion of dopamine at 2.9 $\mu g.kg^{-1}.min^{-1}$.

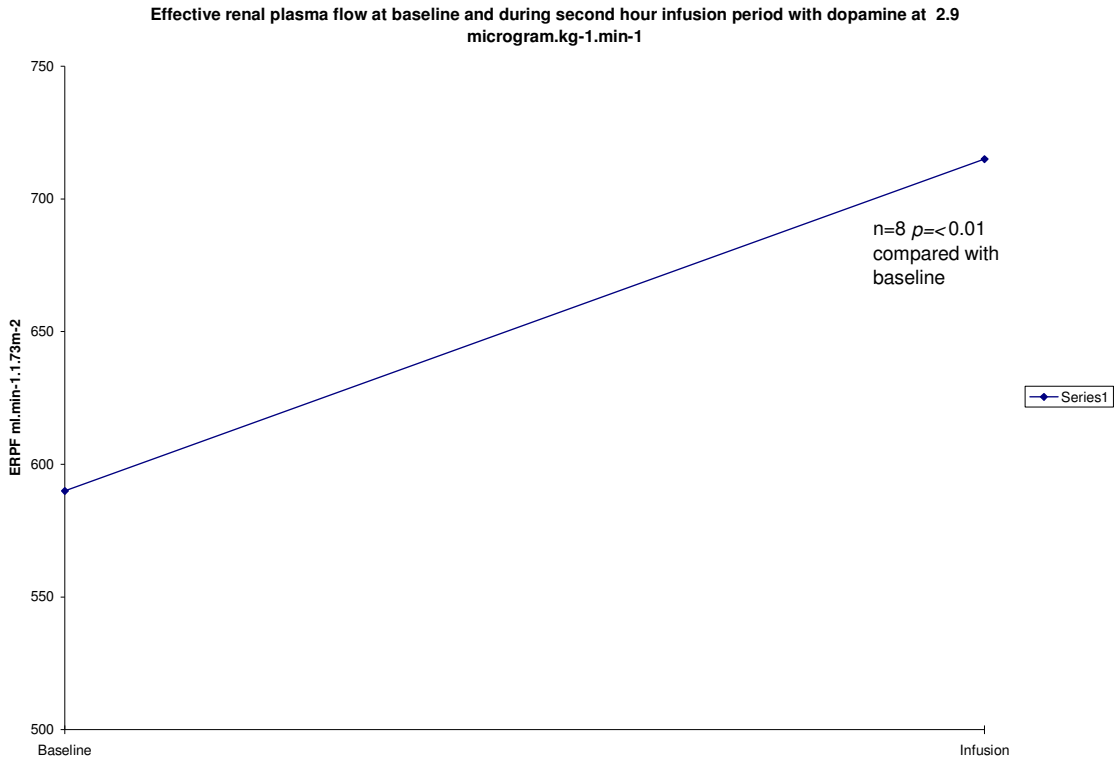


Figure 3

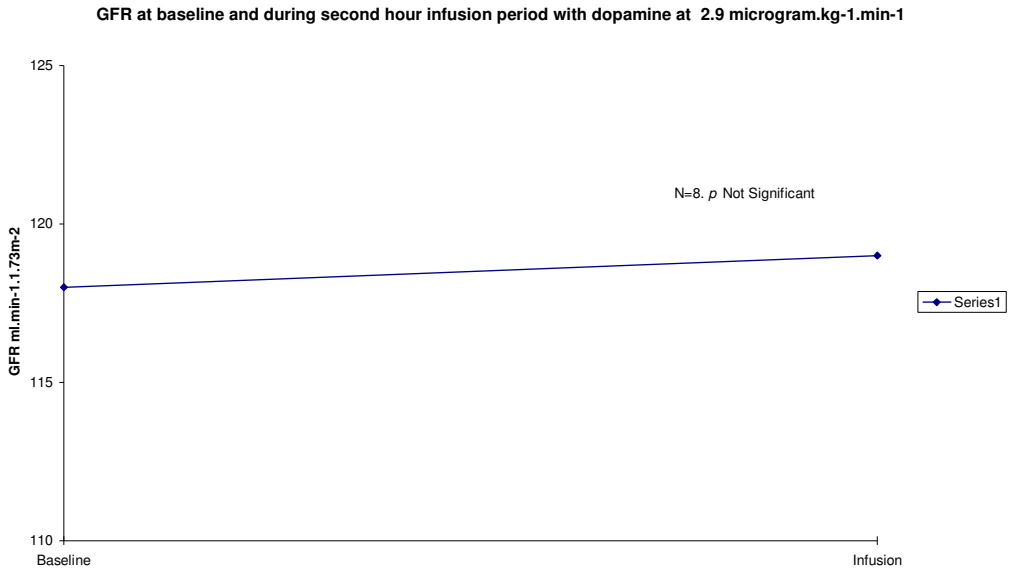


Figure 4

(Figure 3 and Figure 4 both modified from reference 31. Reproduced with kind permission of the publishers. © Lippencott, Williams and Wilkins).

However, no formal studies have been carried out to compare the efficacy in prevention of contrast induced nephropathy with differing doses of dopamine.

Prior to the use of dopamine the accepted way of prevention of ROCIN was adequate rehydration, followed by 500ml of mannitol with 100mg frusemide per 91 μmol/l (1mg/dl) serum creatinine, at a rate of 20 ml/hr for 1 hour prior to and for 6 hours post procedure. Urinary losses were replaced with 5% dextrose with 30 mmol/l of potassium (15).

In other circumstances doses of 0.5 $\mu g.kg^{-1}.min^{-1}$ of dopamine have been used for renal protection (32).

It is current policy in our hospital to use dopamine infused at 2.5 $\mu g.kg^{-1}.min^{-1}$ in the diabetic patients in whom serum creatinine is > 100 μmol/l (> 1.1 mg/dl) for ½ hour prior to and for 6 hours after the procedure.

There has long been controversy about whether - in non diabetics - dopamine works or not in the maintenance of renal perfusion and function [28, 32]. Further differences arise when deciding on the best dose to use in these patients [28, 29].

Various strategies have been tried to help prevent the development of ROCIN. The universal findings so far are those of good hydration and small volumes of low osmolar contrast media. Some authors have advocated a formula for the maximum amount of contrast that should be prescribed to prevent ROCIN. This is shown as a contrast material 'limit'.

$$\frac{\text{5 ml of contrast / kg body weight (maximum 300ml)}}{\text{serum creatinine (mg/dl)}}$$ [12]

Other agents that have been tried are mannitol and frusemide. Both work by trying to increase the intra luminal flow rate and so try to prevent the precipitation of protein / contrast complexes. Prophylactic calcium channel blockers, aminophylline and adenosine are also thought to be useful [33]. However, as they have

not shown definitive benefit, no consensus on their use has been advocated.

The idea of the study was to find out if there is a low dose which still manages to prevent ROCIN. There are, however, a number of problems that some authors have studied. These have, however, been in the main, looking at the use of dopamine in the intensive care setting and so the comparisons may not be valid.

In studies using comparisons with normal subjects and those with uncomplicated insulin dependant diabetes low dose dopamine infusions were responsible for similar increases in GFR and RPF in both groups [7, 34].

It has been suggested that dopamine is not particularly useful for the indication under investigation [28]. In the intensive care setting there have been concerns regarding its potentially adverse effects on respiratory depression [35], pituitary suppression affecting both

anterior and posterior pituitary hormones including prolactin and TSH [36 - 38]. Increased metabolism and gut ischaemia [39] have also limited it's use.

One of the reasons for this is that often these patients are not euvolaemic and so the action of preventing proximal sodium reabsorbtion is counteracted by stronger hormonal and pharmacological influences on these critically ill patients. Conversely, it is for this precise reason that the use of dopamine in patients with heart failure is so effective, it is used in patients effectivly over filled and it promotes sodium loss. It could also be that the higher doses, the β activation causes an increase in cardiac output (and so effective renal blood flow) and this combination is beneficial.

However, the prolonged use of low dose dopamine may make a person hypovolaemic and so at risk of decreasing cardiac output (and so ERBF) putting the kidney at risk of hypoxic damage [40].

Since previous studies have suggested a role for renal vasoconstriction in the pathogenesis of ROCIN then this would suggest that the use of dopexamine as an alternative to dopamine to produce renal vasodilation may be appropriate.

In comparisons between dopexamine 1 - 4 $\mu g.kg^{-1}.min^{-1}$ and dopamine at 2.5 - 10 $\mu g.kg^{-1}.min^{-1}$ both produced a significant dose related increase in renal plasma flow (41). However in the case of dopamine, this reached a plateau at 5 $\mu g.kg^{-1}.min^{-1}$, probably due to α mediated vasoconstriction, this effect was not seen up to 4 $\mu g.kg^{-1}.min^{-1}$ of dopexamine as it is not an α agonist at this (or any) dose. It therefore did not have any significant effect on renal plasma flow. Dopamine at a dose of 3.85 $\mu g.kg^{-1}.min^{-1}$ produces an increased renal plasma flow of 30% (compared with dobutamine at

7.5 $\mu g.kg^{-1}.min^{-1}$ which showed an increase in ERPF of 12% due to an increase in cardiac output) (42). It has also been shown to be effective in renal protection in patients undergoing liver transplantation using dopamine at 2 $\mu g.kg^{-1}.min^{-1}$ (43, 44). However in critically ill patients, the reduced hepatic metabolism of dopamine

may lead to an excess of circulating catacholamine and therefore an excess of α agonist activity and a counter productive vasoconstriction may ensue.

Inferences that may be drawn from this study are that the 2.5 $\mu g.kg^{-1}.min^{-1}$ dose may be better at lowering serum creatinine in the short term, but that at 48 hours this benefit has disappeared. In both groups at 48 hours there was no statistically different change in serum creatinine as compared with the control group. This has to be seen against the background that within the 2.5 $\mu g.kg^{-1}.min^{-1}$ group, 1 patient developed transient renal failure, whilst in the

1 $\mu g.kg^{-1}.min^{-1}$ group none of the patients did.

11.1.Cost implications

A rough estimation for the cost of dopamine used in our institution for this indication at 2.5 $mg.kg^{-1}.min^{-1}$ is £1035 per month. This is worked out by using various assumptions.

Dopamine 400mg vials cost £41.40 per vial [45].

20 vials per month are used on the main diabetes ward for ROCIN prophylaxis at 2.5 $mg.kg^{-1}.min^{-1}$.

The main diabetes ward accounts for 80% of all the angiograms in this group of patients.

This leads to the figure of $\frac{£41.40 \times 20 \times 5}{4}$ = £1035 per month.

However if a simple calculation were applied then at 1 $mg.kg^{-1}.min^{-1}$ then the cost would be £414, however the average volume used also needs some assumptions to be made:

Average weight of patient 70 Kg

Time of dopamine infusion = $6^1/_2$ hours = 390 minutes

@ 2.5 $mg.kg^{-1}.min^{-1}$ = 68.25 mg of dopamine used

@1 $mg.kg^{-1}.min^{-1}$ = 27.30 mg of dopamine used.

BUT dopamine comes in either 200 or 400 mg vials. If the present practice were to continue, then no saving would be made by using the lower dose as the same sized vial would be used. If however - as suggested in a recent editorial regarding bendrofluazide 1.25 mg [46] - pharmaceutical companies could be persuaded to manufacture a more specific formulation / vial size, then a potential saving in cost could be realised.

12. Conclusions

A distinction may be made between a 'statistically significant' result and a 'clinically significant' one. On the basis of this study a change in dopamine dosing for patients with pre existing renal impairment undergoing trans-femoral angiography would not be detrimental to patient care and may lead to a substantial saving in drug costs if drug formulations were changed. The transient decrease in creatinine at 24 hours in the 2.5 $\mu g.kg^{-1}.min^{-1}$ shows an improvement in renal function, however, this may be viewed equally with the

1 $\mu g.kg^{-1}.min^{-1}$ group in whom there was no *worsening* of renal function when compared with the control group.

A change in policy is recommended. In patients presenting with a serum creatinine between 100 mmol/l and 182 mmol/l undergoing femoral angiography a dose of 1 $\mu g.kg^{-1}.min^{-1}$ of dopamine can be used safely as prophylaxis against radio opaque contrast induced renal impairment. The Null Hypothesis is accepted.

13. Graphs

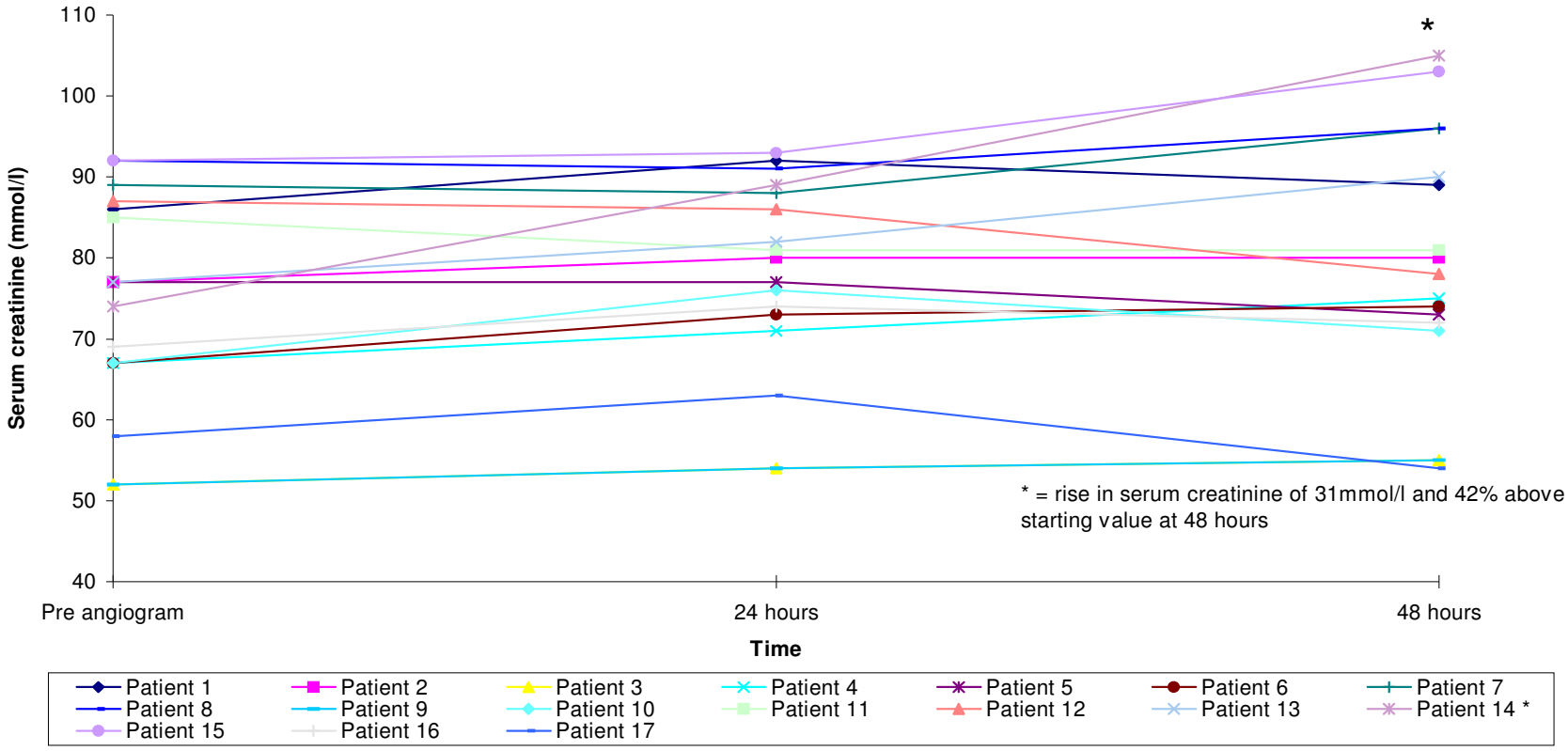
1) Results of serum creatinine in 17 diabetic patients with normal renal function undergoing angiography prior to the procedure, 1 day and 2 days post procedure.

2) Results of serum creatinine in 10 diabetic patients with abnormal renal function undergoing angiography with 2.5 $mg.Kg^{-1}.min^{-1}$ of dopamine prior to the procedure, 1 day and 2 days post procedure.

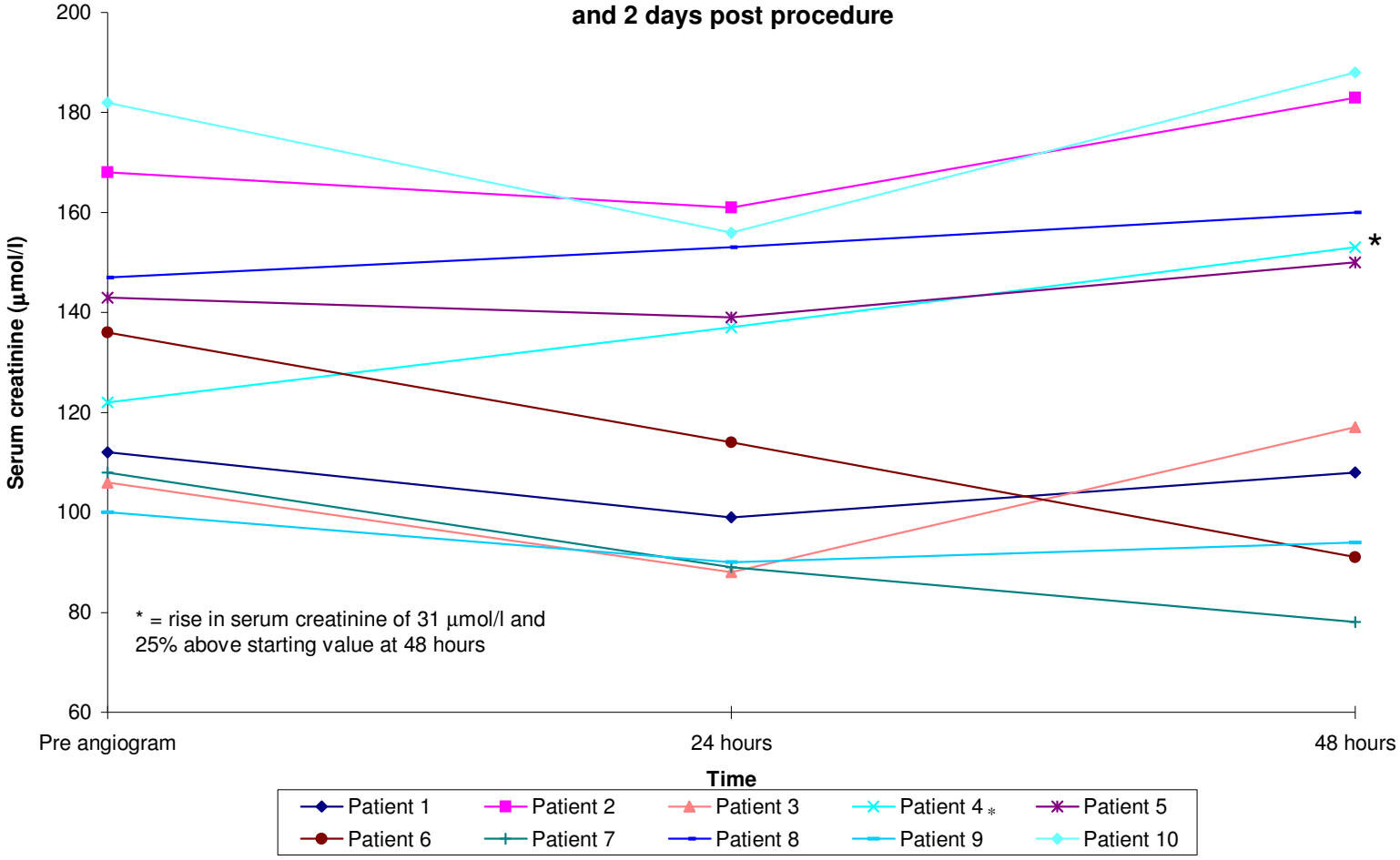
3) Results of serum creatinine in 9 diabetic patients with abnormal renal function undergoing angiography with $1mg.Kg^{-1}.min^{-1}$ of dopamine prior to the procedure, 1 day and 2 days post procedure.

4) Results of serum creatinine in 3 diabetic patients with abnormal renal function undergoing angiography who did not receive dopamine.

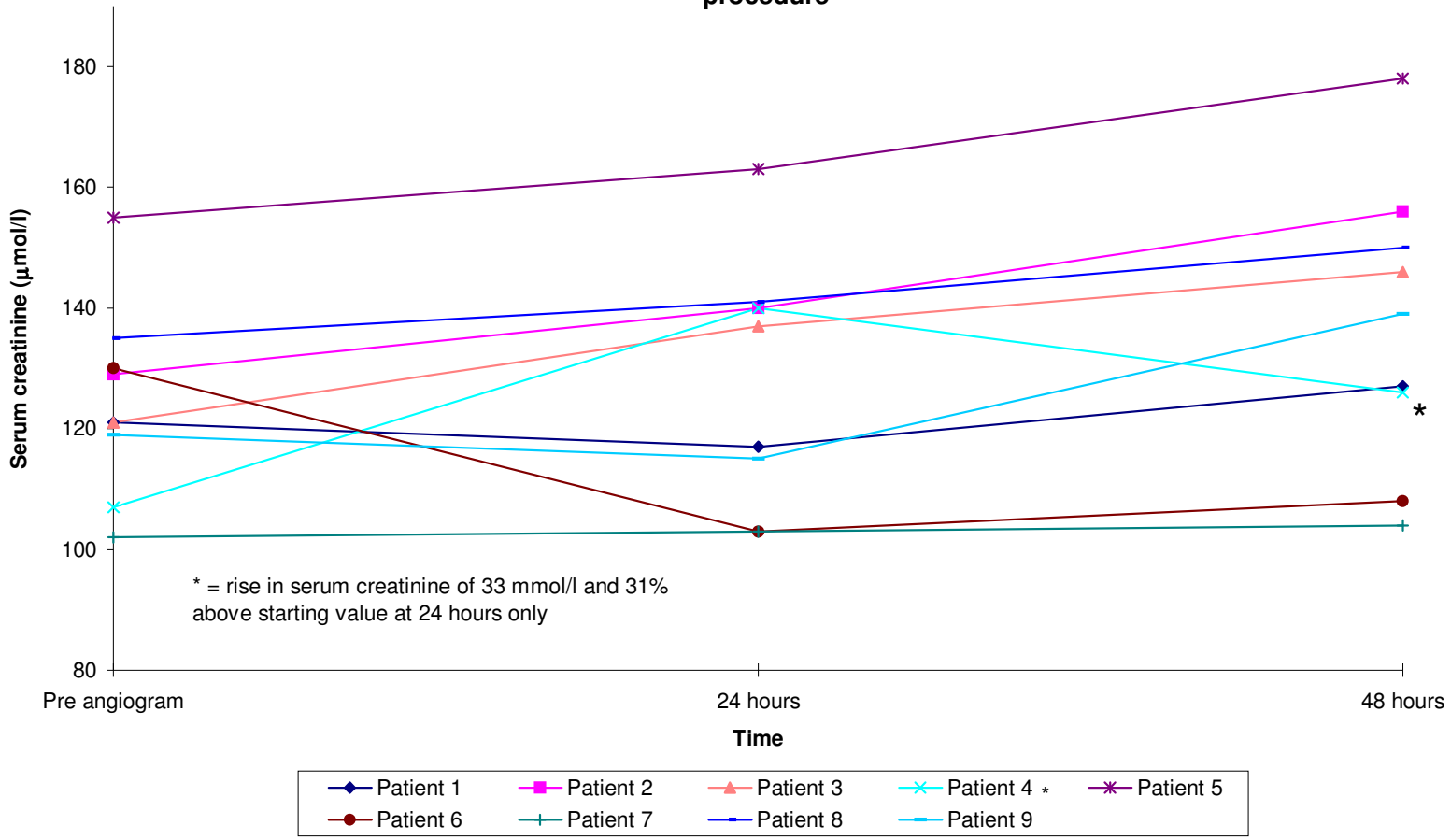
Graph 1 - Results of serum creatinine in 17 diabetic patients with normal renal function undergoing angiography prior to the procedure, 1 day and 2 days post procedure



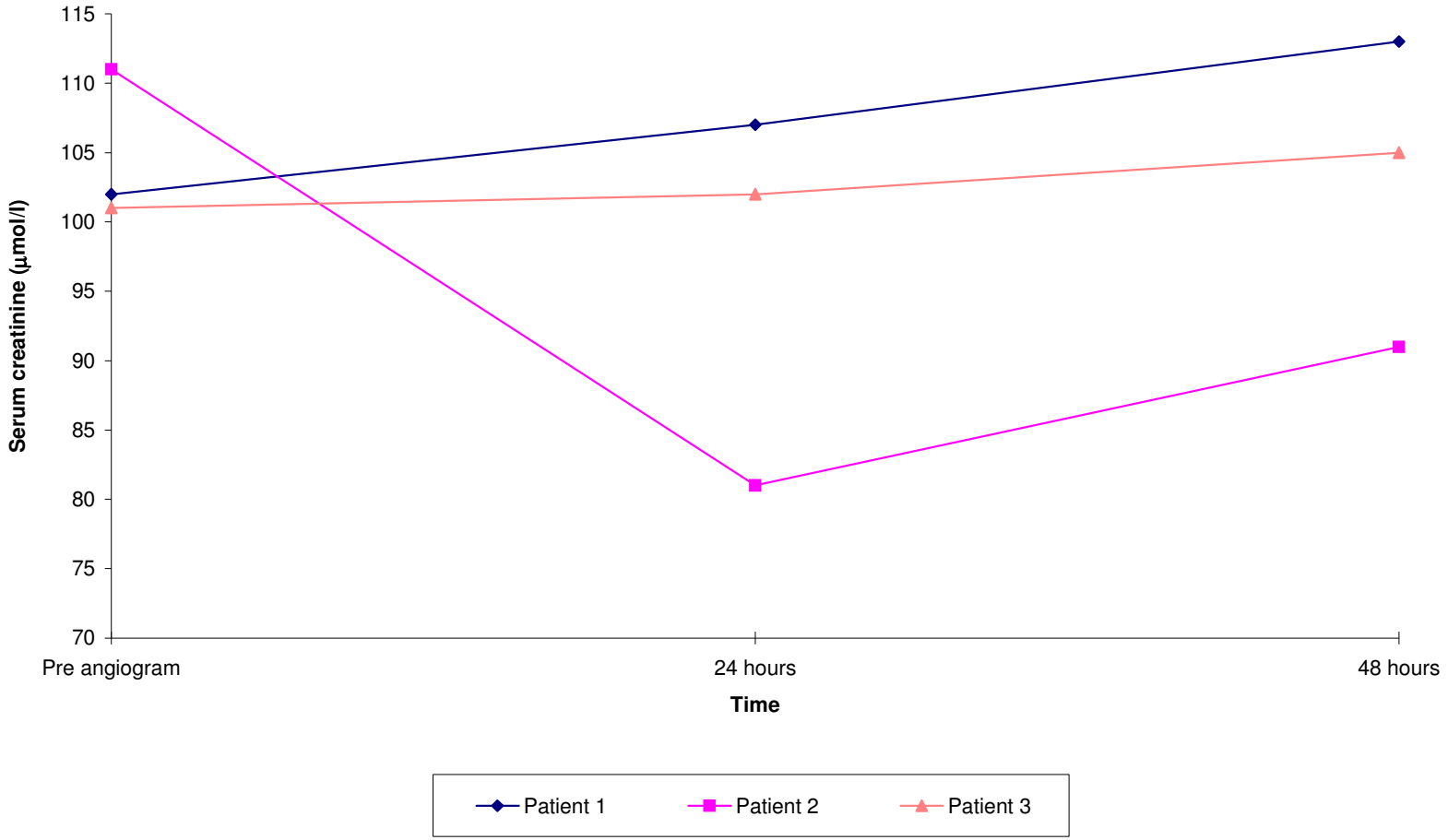
Graph 2 - Results of serum creatinine in 10 diabetic patients with abnormal renal function undergoing angiography with 2.5 microgram.kg-1.min-1 of dopamine prior to the procedure, 1 day and 2 days post procedure



Graph 3 - Results of serum creatinine in 9 diabetic patients with abnormal renal function undergoing angiography with 1 microgram.kg-1.min-1 of dopamine prior to the procedure, 1 day and 2 days post procedure



Graph 4 - Results of serum creatinine in 3 diabetic patients with abnormal renal function undergoing angiography who did not receive dopamine



14. Appendices

Results of serum sodium, potassium, urea and creatinine in 17 diabetic patients with normal renal function undergoing angiography.

Table 2

Patient 1	Day	1	2	3	Patient 10	Day	1	2	3
	Na	130	133	136		Na	136	137	135
	K	3.5	4	4.4		K	4.5	4.6	4.8
	Urea	5.5	4.2	4.8		Urea	8.8	6.1	7.8
	Creat	86	92	89		Creat	67	76	71
Patient 2	Day	1	2	3	Patient 11	Day	1	2	3
	Na	136	131	133		Na	138	140	140
	K	3.8	3.9	4.2		K	4.6	4.3	4.3
	Urea	4.9	4.2	4.9		Urea	-	5.5	6.8
	Creat	77	80	80		Creat	85	81	81
Patient 3	Day	1	2	3	Patient 12	Day	1	2	3
	Na	137	133	131		Na	137	138	136
	K	3.6	5.2	4.7		K	4.2	4.7	4.3
	Urea	4.6	6.8	7.2		Urea	5.3	4.8	3.2
	Creat	52	54	55		Creat	87	86	78
Patient 4	Day	1	2	3	Patient 13	Day	1	2	3
	Na	138	141	141		Na	136	138	136
	K	3.9	3.4	4.1		K	4.2	4.1	4
	Urea	3.6	3.4	5		Urea	4.1	4.2	3.8
	Creat	67	71	75		Creat	77	82	90
Patient 5	Day	1	2	3	Patient 14	Day	1	2	3
	Na	139	138	140		Na	140	139	135
	K	4.9	4.7	4.8		K	4.9	4.7	5.4
	Urea	-	-	5.8		Urea	-	-	-
	Creat	77	77	73		Creat	74	89	105
Patient 6	Day	1	2	3	Patient 15	Day	1	2	3
	Na	134	136	136		Na	136	132	133
	K	4.1	4.5	4.4		K	5	4.7	4.7
	Urea	4.5	-	-		Urea	4.2	3.9	5.9
	Creat	67	73	74		Creat	92	93	103
Patient 7	Day	1	2	3	Patient 16	Day	1	2	3
	Na	133	134	135		Na	140	137	134
	K	5	4.5	4.3		K	4.5	4.4	3.8
	Urea	-	4.7	6.4		Urea	-	3.8	3.5
	Creat	89	88	96		Creat	69	74	72
Patient 8	Day	1	2	3	Patient 17	Day	1	2	3
	Na	133	132	136		Na	130	133	134
	K	4.6	4.7	4.5		K	4.6	4.6	4.6
	Urea	-	-	-		Urea	5.4	7.5	6.7
	Creat	92	91	96		Creat	58	63	54
Patient 9	Day	1	2	3					
	Na	-	139	136					
	K	-	3.7	3.6					
	Urea	-	2.4	2.1					
	Creat	52	54	55					

Units: '-' = data not collected
Na = mmol/l
K = mmol/l
Urea = mmol/l
Creatinine = μmol/l

Results of serum sodium, potassium, urea and creatinine in 10 diabetic patients with abnormal renal function undergoing angiography receiving dopamine at 2.5 $\mu g.kg^{-1}.min^{-1}$

Table 3

Patient 1	Day	1	2	3	Patient 6	Day	1	2	3
	Na	137	135	134		Na	133	137	136
	K	4.5	4.3	4.8		K	5	4.6	4.5
	Urea	5.4	4.9	6		Urea	9.3	7.2	6.7
	Creat	112	99	108		Creat	108	89	78
Patient 2	Day	1	2	3	Patient 7	Day	1	2	3
	Na	137	134	134		Na	133	133	136
	K	3.3	3.9	4.1		K	5.7	5.2	5.3
	Urea	10.2	7.7	8		Urea	9.1	10.1	11.9
	Creat	168	161	183		Creat	147	153	160
Patient 3	Day	1	2	3	Patient 8	Day	1	2	3
	Na	134	134	139		Na	132	130	134
	K	4.4	3.8	4.4		K	4.6	4.3	3.8
	Urea	8.6	7.4	9.4		Urea	-	2.7	-
	Creat	106	88	117		Creat	136	114	91
Patient 4	Day	1	2	3	Patient 9	Day	1	2	3
	Na	132	134	133		Na	136	130	128
	K	5.2	5.1	4.7		K	4.5	4.2	4.3
	Urea	-	10.2	10.1		Urea	17.4	11.3	-
	Creat	122	137	153		Creat	182	156	188
Patient 5	Day	1	2	3	Patient 10	Day	1	2	3
	Na	134	129	133		Na	140	139	141
	K	4.2	4.8	4.4		K	5.3	4	4.8
	Urea	12.2	9.9	10.1		Urea	4.8	5.2	4.8
	Creat	143	139	150		Creat	100	90	94

[Units: '-' = data not collected, Na = mmol/l, K = mmol/l, urea = mmol/l, creatinine = mmol/l]

Results of serum sodium, potassium, urea and creatinine in 9 diabetic patients with abnormal renal function undergoing angiography receiving dopamine at 1 $\mu g.kg^{-1}.min^{-1}$

Table 4

Patient 1	Day	1	2	3	Patient 6	Day	1	2	3
	Na	123	134	142		Na	137	137	139
	K	3.6	4	4.3		K	4.5	4.7	4.2
	Urea	5.9	5.9	5.7		Urea	7.9	7.7	8.8
	Creat	121	117	127		Creat	129	140	156
Patient 2	Day	1	2	3	Patient 7	Day	1	2	3
	Na	137	136	138		Na	138	139	136
	K	4.9	3.9	4.7		K	3.7	4.1	4.5
	Urea	-	7.8	9.6		Urea	-	7.1	8.9
	Creat	121	137	146		Creat	107	140	126
Patient 3	Day	1	2	3	Patient 8	Day	1	2	3
	Na	136	140	141		Na	136	136	139
	K	4.9	5.3	4.5		K	3.7	3.6	2.8
	Urea	8.7	8.6	-		Urea	-	-	4.9
	Creat	155	163	178		Creat	130	103	108
Patient 4	Day	1	2	3	Patient 9	Day	1	2	3
	Na	137	134	134		Na	136	143	137
	K	3.6	3.6	3.8		K	4.4	4.5	4.4
	Urea	5.1	3.9	4		Urea	8.1	7.2	7.4
	Creat	102	103	104		Creat	135	141	150
Patient 5	Day	1	2	3					
	Na	138	136	135					
	K	4.1	3.8	4.1					
	Urea	7.4	8.5	10.6					
	Creat	119	115	139					

[Units: '-' = data not collected, Na = mmol/l, K = mmol/l, urea = mmol/l, creatinine = mmol/l]

Results of serum sodium, potassium, urea and creatinine in 3 diabetic patients with abnormal renal function undergoing angiography who did not receive dopamine.

Table 5

Patient 1	Day	1	2	3	Patient 3	Day	1	2	3
	Na	136	135	135		Na	135	127	135
	K	4.1	4.5	4.4		K	5.3	3.6	4.3
	Urea	6.5	6.3	5.6		Urea	-	-	-
	Creat	102	107	113		Creat	111	81	91
Patient 2	Day	1	2	3					
	Na	133	138	133					
	K	4.8	4.7	4.4					
	Urea	-	-	6					
	Creat	101	102	105					

[

Units: '-' = data not collected, Na = mmol/l, K = mmol/l, urea = mmol/l, creatinine = mmol/l]

These data were not included in the final analysis.

Results of serum sodium, potassium, urea and creatinine in 1 diabetic patient with abnormal renal function undergoing angiography then angioplasty and receiving dopamine at 2.5 $\mu g.kg^{-1}.min^{-1}$

Table 6

Angiogram	Day	1	2	3	Angioplasty	Day	1	2	3
	Na	135	132	134		Na	132	125	127
	K	4.8	4.7	4.9		K	4	3.7	4
	Urea	11.8	12.2	12.8		Urea	17.8	18.4	19.6
	Creat	291	307	317		Creat	360	376	383

[Units:, Na = mmol/l, K = mmol/l, urea = mmol/l, creatinine = mmol/l]

The initial creatinine was higher than that stated in the inclusion criteria and so was not included in the final analysis.

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