A STUDY OF RENAL HAEMODYNAMICS IN CHRONIC LIVER DISEASE

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY OF RENAL HAEMODYNAMICS IN CHRONIC LIVER DISEASE"** submitted by **Dr.K.Muthukumaran**, to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032 Tamilnadu, in partial fulfillment of the requirement for the award of DM., Degree Branch IV (Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

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INTRODUCTION

Several studies of Chronic liver disease have shown that arterial resistance is increased in cirrhotic patients with ascites.It is related to the severity of cirrhosis and to the renal blood flow, aids in predicting progression into hepatorenal syndrome, and is available as a prognostic factor.

The Pulsatility index and resistive index are estimated from blood flow velocity waveform analysis by Doppler studies .They are widely accepted and used as valid indicators of renal vascular resistance. The measurement of renal arterial resistance by doppler has been found to be useful in the study of organic and/or functional renal diseases in cirrhosis. In fact, elegant studies by Kew and colleagues have demonstrated that with the 133Xe washout technique that the renal blood flow is reduced even in well-compensated cirrhosis. Epstein ***et al***. have also shown in their studies with the 133Xe washout technique and renal angiography that mean renal blood flow and renal cortical perfusion are reduced in cirrhotic patients. At present the renal arterial resistance can be easily assessed by measuring the pulsatality index or resistive index with real-time color Doppler studies of renal arteries.

Patients with advanced chronic liver diseases often exhibit an abnormal hemodynamics that is characterized by a hyperdynamic circulation in the splanchnic and systemic areas. Schrier ***et al***. proposed that these homodynamic changes might be due to peripheral hemovasodilatation, which could be recognized even in the very early stage of liver cirrhosis.

The resulting Peripheral vasodilatation and the resulting reduced systemic vascular resistance might contribute to the reduced effective blood flow estimated from blood flow velocity waveform analysis.

REVIEW OF LITERATURE

A normal perfusion of the kidneys is crucial to the maintenance of kidney functions, including not only glomerular filtration rate (GFR) but also excretory functions. Under normal physiological conditions, the renal blood flow is maintained constant through maintenance of a delicate equilibrium between the level of vasoconstrictors and the vasodilating factors acting on the renal circulation in such a way that any increase in the activity of vasoconstrictor factors is rapidly followed by a increase in compensatory activation of the renal vasodilators, which helps to maintain the renal perfusion within normal limits.

Renal hemodynamics in cirrhosis

It has been known for many years that such equilibrium in the renal circulation is of crucial importance in the setting of cirrhosis. In some pathological instances, the equilibrium in the renal circulation can no longer be maintained, so that there is predominance of vasoconstrictor factors and reduction in renal perfusion occurs.

Investigations performed by several group of investigators between the 1950s and 1970s using specific methods to assess renal plasma flow and GFR provided conclusive evidence of a reduced renal perfusion and GFR in patients with advanced cirrhosis. They have also conclusively demonstrated that hepatorenal syndrome (HRS) was due to a vasoconstriction of the renal circulation.

Later studies showed that patients with even less advanced degree cirrhosis may also have some degree of renal vasoconstriction that tends to progress over time. While some of the patients with pre-ascitic cirrhosis may have normal renal perfusion with no evidence of renal vasoconstriction, Most of the patients with ascites show a significant reduction of renal blood

flow and glomerular filtration rate of variable degrees that usually follow other abnormalities of renal function such as sodium and solute-free water retention that are further impaired by the reduction in GFR.

MECHANISMS INVOLVED IN THE REGULATION OF RENAL HEMODYNAMICS IN CIRRHOSIS

The exact mechanisms leading to renal vasoconstriction in cirrhosis are not completely known. Several factors, including disturbances in systemic hemodynamics, increased activity of vasoconstrictor systems, and reduced activity of vasodilator factors acting on the renal circulation play a major role.

The hemodynamic pattern of patients with HRS is characterized by hypervolemia, high cardiac output, low arterial pressure and total systemic vascular resistance, and marked activation of vasoconstrictor systems.

This pattern of highly increased renal vascular resistance in the setting of low total systemic vascular resistance and compensatory over activity of vasoconstrictor systems is very characteristic of HRS, although not exclusive, as it may be observed in renal failure associated with sepsis.

By contrast, this pattern is markedly different from that of hypovolemia, low cardiac output, and high total systemic vascular resistance characteristic of most clinical conditions associated with renal hypo perfusion of prerenal origin.

Rennin–Angiotensin–Aldosterone System

The rennin–angiotensin–aldosterone system (RAAS) was the first major vasoconstrictor system to be investigated as a possible factor responsible for renal vasoconstriction in cirrhosis. It is now well known that the activation of RAAS is particularly intense in patients with HRS compared with patients with cirrhosis and ascites without HRS. Moreover, there is an inverse relationship between the plasma rennin activity (PRA), which estimates the activity of the RAAS, and the renal plasma flow and GFR.

Further more the indirect evidence for the role of the RAAS in the pathogenesis of renal vasoconstriction in HRS derives from clinical studies showing that treatment of patients with HRS with vasoconstrictor drugs and albumin or transjugular intrahepatic portosystemic shunts (TIPS) is followed by a marked improvement of renal plasma flow and GFR that occurs together with a marked suppression (complete normalization in some cases)of the increased activity of the rennin angiotensin system. An additional piece of evidence supporting the role of the RAAS in the pathogenesis of HRS derives from the assessment of evolution of the temporal relationship between the activation of the RAAS and the development of renal failure in patients with cirrhosis and spontaneous bacterial peritonitis In this condition, the development of HRS is associated with a striking activation of the RAAS.

The prompt administration of intravenous albumin also prevents the activation of Rennin angiotensin aldosterone system during the infection and reduces the rate of development of HRS.

Interestingly,some of the recent studies have shown that the beneficial effect of albumin in this setting is perhaps due to an increase both in total systemic vascular resistance and in cardiac output. Despite all this indirect evidence, the definite confirmation of a role for the RAAS in the pathogenesis of renal vasoconstriction in cirrhosis has not been provided and may be impossible. This would require the demonstration that the pharmacological interruption of the

RAAS activity is ssociated with a reversal of the renal vasoconstriction. Unfortunately, this approach cannot be used in our clinical practice, as the blockade of the activity of the RAAS is associated with marked arterial hypotension in patients with cirrhosis and ascites, due to the important effect of the RAAS in the maintenance of arterial pressure in this condition.

SYMPATHETIC NERVOUS SYSTEM

As occurs with the RAAS, in cases of advanced cirrhosis there is an increased activity of the sympathetic nervous system (SNS).The plasma concentration of vasoconstrictor norepinephrine (NE) in the systemic circulation, an index of the activity of the SNS, is increased in most patients with ascites and normal or only slightly elevated in patients without ascites.

Because the SNS is one of the powerful vasoconstrictor of the renal circulation it would be reasonable to presume that the increased renal sympathetic nervous activity in cirrhosis may be important factor in the pathogenesis of renal vasoconstriction and also in HRS.

In fact, patients with HRS have significantly higher plasma levels of Norepinephrine than cirrhotic patients with ascites without renal failure. The peripheral venous, arterial, and renal venous norepinephrine levels correlate inversely with renal blood. Further evidence in favor of the participation of the sympathetic nervous system (SNS) in the pathogenesis of the HRS is that the improvement in renal blood flow and GFR after pharmacological treatment with vasoconstrictor drugs.TIPS placement in patients with HRS is paralleled by a marked suppression of the activity of the SNS.

Unfortunately, in the same way as occurs with the RAAS,the inhibition of SNS activity in patients with cirrhosis, using the central 2-adrenergic clonidine, is associated with a marked fall in arterial pressure, which makes it impossible to test directly whether the SNS plays a major

role in development of renal vasoconstriction in cirrhosis .

One the recent observation that the administration of norepinephrine intravenously together with albumin improves renal function in patients with Hepato renal syndrome has cast some doubt on the role of the endogenous Norepinephrine as renal vasoconstrictor in HRS. Nevertheless, it appears that exogenous NE produces renal vasoconstriction only when it is given directly into the renal artery or at doses that produce arterial hypertension.

NeuropeptideY is a neurotransmitter which has with a potent renal vasoconstrictor effect that is released in the setting of a marked activation of the SNS, may also have a role as renal vasoconstrictor in cirrhosis, as peripheral plasma levels of NeuropeptideY are increased in patients with HRS but not in patients with ascites without renal failure.

ENDOTHELINS

The endothelin family comprises of three homologous peptides synthesized by a number of cell types, including the endothelial cells found in the systemic arterial and venous circulation.

The sinusoidal endothelial cells and the hepatic stellate cells found liver, and also the mesangial cells in kidney synthesize endothelins. The effects of Endothelins are mediated through two types of receptors, ETA and ETB, that exhibit distinct selectivity for ET isopeptides. The ETA receptor binds ET-1 and ET-2 with a higher affinity than ET-3, while ETB displays similar affinities for all three isopeptides.

ETA is responsible for the vasoconstrictor effect of ETs, whereas the stimulation of ETB causes mainly vasodilatation through the activation of nitric oxide (NO) and prostaglandins.

ET synthesized by endothelial cells is thought to participate in the regulation of

vascular tone by acting as a paracrine substance on the underlying vascular smooth muscle cells.Most of the patients with cirrhosis of liver have increased circulating levels of endothelins(ET).Because of this and its marked vasoconstrictor effect, it has been proposed that ET contributes to the pathogenesis of renal vasoconstriction in cirrhosis. An inverse relationship between plasma levels of ET and renal plasma flow and GFR has been demonstrated in patients with ascites in some but not all studies. However, the correlation between plasma levels of ET and renal function is weak in most studies. Moreover there is no consistent relationship between plasma levels of ET and the presence or absence of HRS.

Nevertheless, it should be emphasized that because endothelins are substance with a paracrine mode of action, its plasma levels do not necessarily reflect levels of ET within the kidney, which so far have not been measured in human cirrhosis. Interestingly, improvement of renal function was reported in a small group of patient's withHRS after administration of BQ-123, selective antagonist of ETA receptors.

Unfortunately, this interesting finding has not been followed by studies in larger groups of patients. In summary, a role for ET in the pathogenesis of HRS is possible but has not been demonstrated thus far. This confirmation awaits studies using newly developed ET receptor antagonists in patients with HRS.

ADENOSINE

Adenosine is an adenosine triphosphate (ATP) breakdown product that causes vasodilatation in most of most of the vessels and contributes to the metabolic control of organ perfusion. In contrast to its vasodilatory effect in other organs, adenosine produces vasoconstriction in the renal vasculature. For this reason, adenosine has been investigated as possible mediator of renal vasoconstriction in cirrhosis.Adenosine-1 receptors are present on the afferent arteriole in the kidney and cells of the

proximal tubule and stimulation of these receptors inhibit adenylcyclase activity, resulting in renal vasoconstriction.It also causes sodium and water retention.

Adenosine-2 receptors are found in the vasculature of the systemic circulation and their stimulation leads to vasodilatation.

The possible roles of adenosine in the pathogenesis of renal functional abnormalities in human cirrhosis have been assessed using several pharmacological approaches. These studies have shown that acute administration of methylxanthines, which act as nonspecific adenosine antagonists, to patients with cirrhosis and ascites is associated with an increase in the renal blood flow, Glomerular filtration rate and sodium and water excretion while the acute administration of an adenosine-1 receptor antagonist to patients with cirrhosis and ascites induces a marked increase in sodium excretion and urine flow, without significant changes in renal hemodynamics.

Conversely, the acute administration of dipyridamole,a drug that acts, at least in part, by increasing the levels of adenosine in the extra cellular fluid due to inhibition of the cellular uptake of this substance, It is associated with renal vasoconstriction and increased sodium and water retention, particularly in those patients with ascites and increased activity of the RAAS Taken together, these results indicate that adenosine may have a role in renal vasoconstriction and associated renal abnormalities of cirrhosis.

Vasoconstrictor Eicosanoids

In addition to synthesis of the vasodilating prostaglandins, the kidney also synthesizes a number of vasoactive eicosanoids which have antinatriuretic and/or vasoconstrictor activities. The renal production of some of these eicosanoids with vasoconstrictor activity has also been investigated in patients with cirrhosis. It was first suggested that HRS could be the consequence of an imbalance between the renal synthesis of vasodilator and vasoconstrictor

eicosanoids based on the observation of reduced urinary excretion of prostaglandin E2 (PGE2) and 6-keto-PGF1[a metabolite of prostaglandin I2 (PGI2)] and increased urinary excretion of thromboxanes (i.e. TXB2) in patients with HRS.

These findings however were not confirmed by any of subsequent investigations in which the urinary excretion of thrombaxane B2 in patients with HRS was found to be decreased. Moreover the inhibition of thromboxanes synthesis does not seem toimprove the renal function in these patients.

The Eicosanoids other than thromboxanes with their vasoconstrictor effect may potentially participate in the reduction of renal perfusion in cirrhosis. The possible role of leukotrienes (LTs) in HRS has been somehow overlooked.

Indeed, studies performed in the late 1980s and early 1990s have showed that the urinary excretion of LTE4, the major metabolite of LTC4, andLTD4, and a useful measure of whole body production of cysteinyl-leukotrienes, is elevated in HRS.

More recently,the concentration of the vasoconstrictor metabolite 20-hydroxyeicosatetraenoicacid has been shown to be markedly increased in the urine of patients with cirrhosis and ascites and inversely correlated with renal blood flow.

Finally, the possible role of a family of newly discovered vasoactive peptides, prostaglandin F2-like compounds, termed F2-isoprostanes, that are produced in vivo as products of free radical catalyzed lipid peroxidation independent of action of cyclooxygenase enzyme, has been explored.

Patients with HRS have markedly increased plasma levels of F2-isoprostanes in the peripheral blood compared with those of patients with decompensated liver disease without renal failure and patients with chronic renal failure without liver disease.

The potential role of all these vasoconstrictor eicosanoids in the pathogenesis of renal vasoconstriction in cirrhosis deserves further investigation.

RENAL VASODILATORS

PROSTAGLANDINS

Prostaglandins have a important protective effect on renal function in pathophysiological conditions, such as cirrhosis with ascites,which associated with increased activity of renal vasoconstrictor systems number of studies in patients with cirrhosis have provided data supporting the existence of an renal synthesis of PGs.

Urinary excretion of the prostaglandin E2 and that of 6-keto-prostaglandin F1, which are the estimates the renal synthesis of PGE2 and PGI2, respectively are increased in patients with cirrhosis and ascites without renal failure compared with healthy subjects and patients without ascites.

Studies done with experimental cirrhosis have extended these observations, showing an increased activity and expression of cytosolic phospholipaseA2 and cyclooxygenase (COX), the important two enzymes of the metabolic cascade of eicosanoids synthesis.

Out of the two isoforms of COX, only COX-2, the inducible isoform, is over expressed inthe kidneys of rats with carbon tetrachloride-induced cirrhosis, while the constitutive COX-1 is expressed normally. Nevertheless, COX-1 may be more important for the maintenance of optimal renal function. This is because selective inhibition of cox1 in rats with cirrhosis is associated with impairment in renal function, while the selective inhibition of COX-2 isoenzyme does not cause significant effects on renal function.

No validated data are available on level of the expression and the activities of the different COX isoforms in human cirrhosis. The supports for the important role of renal prostoglandins (PGs) in the optimal maintenance of renal blood flow and GFR in cirrhosis with ascites are derived from studies assessing the effects of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit renal PG synthesis.

The administration of classic NSAIDs, which cause a nonselective inhibition of COX activity, even in single doses, to cirrhotic patients with ascites causes a profound decrease in renal blood flow and GFR, particularly in patients with over activity of endogenous vasoconstrictor systems .In clinical practice these are actually patients with marked sodium retention requiring continuous administration of moderate or high doses of diuretics. Therefore, NSAIDs should not be given to patients with cirrhosis and moderate or severe ascites.

Classic NSAIDs have little or no effect on renal blood flow and GFR in patients without ascites or with ascites but without over activity of vasoconstrictor systems. However, in these patients the administration of NSAIDs may impair sodium excretion and lead to the development of ascites or increase ascites volume (P. Ginès, unpublished data).

Besides, inhibition of prostoglandins synthesis may also impair solute-free water excretion and lead to the development of dilutional hyponatremia.

Therefore, the use of classic NSAIDs should be avoided in all patients with cirrhosis. The available information on the renal effects of drugs that inhibit selectively COX-2 activity in patients with cirrhosis and ascites is very limited.

Two recent studies show that the administration of these drugs to patients with cirrhosis and ascites is not associated with any deleterious effects on renal function. However in these studies

drugs were given for a short period of time.

Therefore, the effects of prolonged selective COX-2 inhibition on renal function in cirrhosis with ascites remain to be established. Following the demonstration of an increased renal production of PGs and their participation in the maintenance of renal function in cirrhosis and ascites.It was proposed that the low GFR characteristic of HRS could be consequence of a spontaneous reduction in renal PG synthesis.

Several studies have reported that patients with HRS have lower urinary excretion of PGE2 and 6-keto-PGF1 thạn do patients with ascites without renal failure while other studies reported a normal urinary excretion of vasodilator prostoglandins in patients with HRS. Nevertheless,even a "normal" synthesis of Prostoglandins may below the optimal level relative to he increased activity of vasoconstrictor systems present in cirrhosis.

Because patients with HRS have the greatest activation of renal vasoconstrictor systems, an imbalance between the production vasoconstrictor systems and the renal production of vasodilator PGs could account, at least in part, for the marked reduction of renal blood flow and GFR that occur in this condition.

NATRIURETIC FACTORS

There is clear evidence for an increased production of peptides from the natriuretic peptide family (atrial natriuretic peptide,brain natriuretic peptide,and the Cnatriuretic peptide) in the setting of cirrhosis, particularly in patients with ascites. Since the major biological effect of these peptides is to increase the renal excretion of sodium, a role of these peptides in the pathogenesis of sodium retention in cirrhosis has been proposed.

Because these peptides also have also vasodilator properties, they could participate in the

pathogenesis of arterial vasodilatation and maintenance of renal perfusion. Data from studies in experimental cirrhosis suggests that they play an important role in the maintenance of renal perfusion and modulation of RAAS activity. In fact the selective blockade of the natriuretic peptide A and B receptors causes renal vasoconstriction and increased PRA and aldosterone levels in rats with cirrhosis and ascites.

No data are available on the effects of inhibition or antagonism of natriuretic peptides in human cirrhosis. Therefore the possible role of these peptides to counteract the activity of renal vasoconstrictor systems remains speculative.

NITRIC OXIDE

NO has been extensively studied as potential mediator of arterial vasodilatation in cirrhosis. There is experimental evidence indicating that the production of NO is increased in the kidney of rats with cirrhosis, because kidneys from cirrhotic rats have an enhanced endothelium-dependent vasodilator response compared with control animals and infusion of L-arginine, the precursor of NO causes a greater increase in renal perfusion in cirrhotic rats compared with controls. Increased expression of NO synthase (NOS) in kidney from cirrhotic rats has been demonstrated in two studies, but there is disagreement on the isoforms of NOS responsible for the increased synthesis of NO.

The importance of this increased renal production of NO in experimental cirrhosis is not known. Inhibition of NO in this setting does not cause renal hypoperfusion, but it is associated with an increased synthesis of PGs.By contrast, simultaneous inhibition of NO and PGs results in marked renal vasoconstriction. Therefore it is possible that NO interacts with PGs to maintain the renal hemodynamics in experimental cirrhosis.

No information is available on renal NO production and its possible role in the modulation

of renal function in human cirrhosis.

RENAL KALLIKREIN–KININ SYSTEM

Some studies have reported that urinary kallikrein excretion is increased in patients with ascites without renal failure and reduced in patients with HRS and correlates directly with GFR, suggesting the role of renal kallikrein–kinin system. It is an intrarenal system with vasodilator and natriuretic activities, which may contribute to the maintenance of renal hemodynamics in cirrhosis.

Other investigations however have found reduced urinary kallikrein excretion in patients with ascites.Much more specific methods to evaluate the activity of the kallikrein–kinin system are needed before the role of this system in the homeostasis of renal function in cirrhosis can be defined.

PATHOGENESIS OF HEPATORENAL SYNDROME

The pathophysiological hallmark of HRS is a severe vasoconstriction of the renal circulation. Any theory that aim's at explaining the pathogenesis of HRS should provide an explanation for the existence of a marked renal vasoconstriction in the setting of a very pronounced arterial under filling in the systemic circulation which is characteristic of cirrhosis. In addition, it should also provide an explanation for the continuum from compensated cirrhosis with normal or near-normal renal function to decompensated cirrhosis with ascites and sodium retention, severely decompensated cirrhosis with severe ascites and spontaneous dilutional hyponatremia and finally renal failure due to renal vasoconstriction (i.e. HRS).

The theory that best fits with the observed alterations in the renal and circulatory function in HRS is the arterial vasodilatation theory, which proposes that HRS is the result of the effect of vasoconstrictor systems acting on the renal circulation. These constrictor systems are activated as homeostatic mechanisms to counteract the extreme under filling of the arterial circulation and thus to

maintain arterial pressure. As a result of this increased activity of the vasoconstrictor systems, renal perfusion and GFR are markedly reduced but tubular function is preserved.

This is different from what occurs in acute tubular necrosis (ATN), in which renal failure is associated with a markedly impaired tubular function. The activated vasoconstrictor systems are also responsible for the sodium retention and impaired solute-free water excretion that occur in the setting of HRS .Most available data suggest that arterial under filling is due to a marked vasodilatation of the splanchnic circulation related to an increased splanchnic production of vasodilator substances, particularly NO Sodium retention and ascites and edema formation would develop as a consequence of homeostatic activation of vasoconstrictor and antinatriuretic mechanisms acting on the systemic circulation and kidneys to maintain effective arterial blood volume constant. In initial phases of decompensated cirrhosis, renal perfusion would be maintained within normal levels despite the activation of potent vasoconstrictor factors because of an increased synthesis of renal vasodilators (mainly prostaglandins).

In this setting, the equilibrium between vasoconstrictor and vasodilator factors is very delicate and the kidney is very sensitive to further impairment in the systemic arterial circulation and/or decreases in the renal production of vasodilator factors.

Therefore, any impairment in arterial under filling, either spontaneous, due to progression of splanchnic vasodilatation, or triggered by specific clinical circumstances (i.e. bacterial infections, especially spontaneous bacterial peritonitis, large-volume paracentesis without plasma expansion or gastrointestinal bleeding) would result in a further activation of vasoconstrictor systems.The splanchnic area would escape from the effect of vasoconstrictors probably because of a markedly enhanced local production of vasodilators.

The recent observation by several groups that the administration of vasoconstrictor drugs with a

preferential effect on the splanchnic circulation, such as ornipresin or terlipressin,together with albumin administration improves renal function in patients with HRS is consistent with series of events proposed by the arterial vasodilatation hypothesis.

Although arterial under filling in HRS is mainly due to splanchnic arterial vasodilatation causing an abnormal distribution of arterial blood volume, recent evidence suggests that an impaired cardiac function due to cirrhotic cardiomyopathy may also play a role.

Although cardiac output is high in most patients with HRS, it may be low relative to markedly dilated splanchnic vascular bed. It has been proposed that a reduction in cardiac output from the high values characteristic of cirrhosis with ascites to normal or moderately reduced values may trigger the development of HRS, particularly type 1.The possible role of impaired cardiac function in the pathogenesis of HRS should be investigated further. Vasoconstriction of the renal circulation is a common finding in patients with cirrhosis.It may already occur in early stages of the disease, but it becomes more marked over time. In most patients, marked vasoconstriction of the renal circulation occurs after patients have developed an impaired excretion of sodium and solute-free water (which are manifested clinically by development of ascites and dilutional hyponatremia, respectively).

It is now well established that vasoconstriction of the renal circulation occurs as a consequence of a marked impairment of the systemic arterial circulation.It is characterized by arterial vasodilatation, which predominates in the splanchnic area, and compensatory activation of the endogenous vasoconstrictor systems. These activated vasoconstrictor systems cause an effect on the kidneycirculation, whichis roughly proportionate to their degree of activation.

Vasodilators of renal and extra renal origin are subsequently activated to compensate for the increased activity of vasoconstrictor factors in the kidney. This situation results in a very delicate equilibrium in the renal circulation, which is then very sensitive to changes in the activity of vasoactive

factors. Either an increase in the activity of vasoconstrictor factors (generally as a result of a further impairment in the systemic arterial circulation) or a decrease in the activity of vasodilator factors may lead to the development of HRS, which is the extreme expression of renal vasoconstriction in the kidney.

RENAL DOPPLER ULTRASOUND

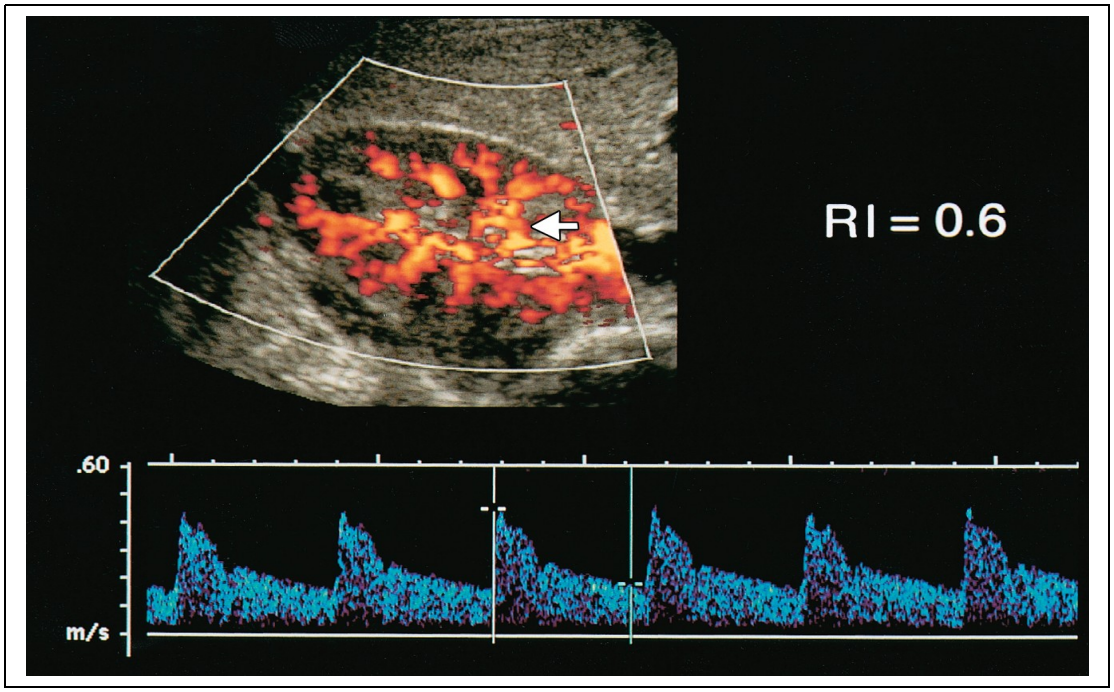
A series of articles published during the past decade clearly indicated the potential of doppler sonography for improving the sonographic assessment of renal dysfunction. Changes in intrarenal arterial waveforms were shown to be associated with urinary obstruction, several types of intrinsic renal disorders, and renal vascular disease.

The Doppler resistive index (RI) = ([peaksystolicvelocity– end diastolic velocity] / peak systolic velocity) was advanced as a useful parameter for quantifying the alterations in renal blood flow that may occur with renal disease.

TECHNIQUE

Most studies describing the potential use of Doppler sonographic for evaluating renal disease have stressed the need for meticulous technique. The highest frequency probe that gives measurable waveforms should be preferentially used, supplemented by color or power Doppler sonography as necessary for vessel localization. Arcuate arteries (at the corticomedullary junction) or interlobar arteries (adjacent to medullary pyramids) are then insonated using a 2- to4-mm Doppler gate. Waveforms should be optimized for measurement using the lowest pulse repetition frequency without aliasing (to maximize waveform size), the highest gain without obscuring background noise, and the lowest wall filter.

About three to five reproducible waveforms from each kidney are obtained, and the RIs from these waveforms are averaged to arrive at mean RI values for each



THEORY OF RI

The earlier failure of the RI to become a meaningful parameter for evaluating kidney physiology and function may be due to our often rudimentary understanding of renal disease.Furthermore Doppler sonographic analysis of renal artery waveforms was empirically applied to disease characterization before a full understanding of the factors that affect the arterial waveform (e.g., vascular compliance, vascular résistance, and heart rate) was obtained.Thus,this empiric use of Doppler sonography gave less than satisfactory results.

For example,it was almost universally accepted in the early Doppler literature that the RI varied directly with changes in renal vascular resistance. In many reports, the both terms “resistive index” and “renal vascular resistance” are used interchangeably.

Although the relationship between these factors and other potentially confounding variables have generally not been considered. A series of in vitro experiments recently performed at the University of Michigan have convincingly shown the important role of vascular compliance in RI analysis. Compliance is the rate of change of volume of a vessel as a function of pressure.

Anyone who has observed a pulsating artery whose diameter expands in systole and contracts in diastole has seen the visual manifestation of the effect of compliance. In vitro experiments were performed to assess the impact of changes in vascular resistance and compliance on the RI.

The RI was dependent on the vascular compliance and resistance, becoming less and less dependent on resistance as the compliance decreased, and being completely independent of vascular resistance when compliance was zero. In another in vitro study performed by the same group of investigators, the RI was shown to decrease with increases in the cross-sectional area of the distal arterial bed; this effect was independent of compliance and vascular resistance.

Ex vivo results, similar to in vitro results, were obtained in a series of experiments performed at Albany Medical College. Rabbit kidneys were perfused ex vivo using a pulsatile perfusion system (Fig. 3). Renal vascular resistance, systole, diastole, pulse pressure, and pulse rate were controlled and monitored while the RI was simultaneously measured.

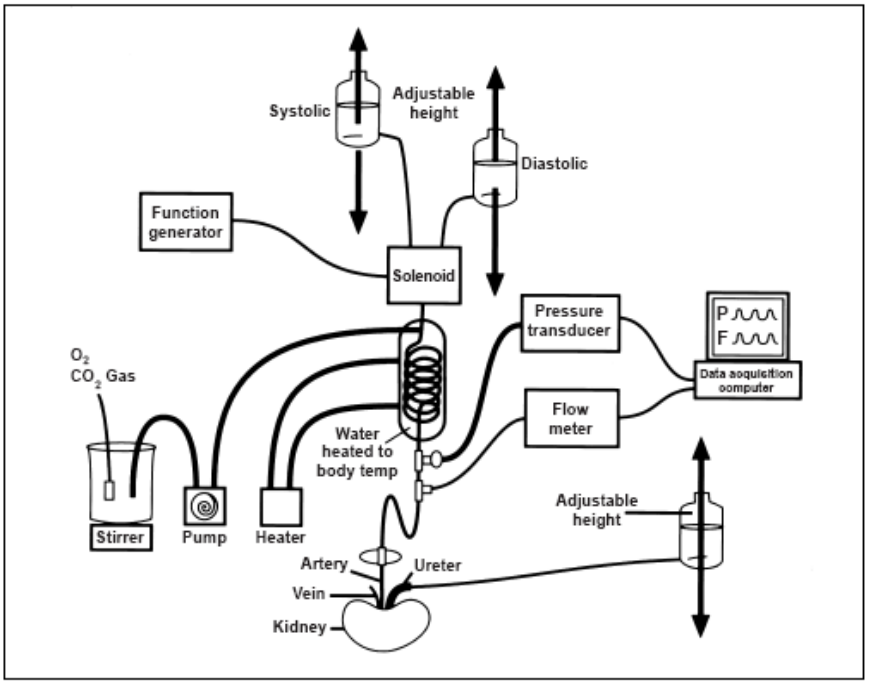


Fig. 3.—Diagram of ex vivo pulsatile perfusion system. Perfusion pressures (systole and diastole) are adjusted by changing heights of reservoirs, and pulse rate is controlled by function generator. Flow (F) and pressure (P) are measured instantaneously upstream from renal artery using in-line probes. Doppler spectra are simultaneously obtained from perfused kidney using commercially available ultrasound platform. Temp = temperature. (Reprinted with permission from [94])

A linear relationship was seen between the RI and pharmacologically induced changes in renal vascular resistance. However, the RI increased only with very marked, likely nonphysiologic increases in renal vascular résistance. Those changes in the RI that were seen with intense vasoconstriction were only marginally greater than RI measurement variability. The RI was also markedly affected by changes in driving pulse pressures, however. A linear relationship was shown between the pulse pressure index (systolic pressure – diastolic pressure / systolic pressure) and the RI.

AIM OF THE STUDY

1. To calculate the renal arterial Resistive index, Pulsatility index in patients with chronic liver disease.
2. To calculate renal arterial RI index in patients with chronic liver disease and its correlation with severity of chronic Liver disease.
3. To study the usefulness of RI as a noninvasive predictor of response to diuretic therapy in chronic liver disease.
4. To study renal arterial resistive index and its association with esophageal varices in patients with chronic liver disease.

METHODS AND MATERIALS

The study was conducted between January 2006 and May 2008 in Government peripheral hospital, Annanagar.The study was a prospective study.

INCLUSION CRITERIA

Patient who were diagnosed to have cirrhosis by combination of clinical, biochemical, endoscopic and histological features and who are off diuretics for two weeks.

New patients who were diagnosed to have cirrhosis by combination of Clinical, radiological, and histological features.

EXCLUSION CRITERIA

a. Patients with intrinsic renal disease, Diabetes mellitus, Hypertension.

b. Patients with active GI bleed, infections, malignancy.

c. Patients with CLD who had taken diuretic within a fortnight.

d. Patients with serum creatinine > 1.4mg.

Detailed history was taken from the patients and a complete physical examination of patients was carried out. In particular attention was paid to look for signs of liver cell

failure like the spider, palmar erythema, and parotid enlargement, palmar erythema, Duptyrene contractions.

A careful examination of abdomen was done to look for hepatomegaly and spleenomegaly, ascites.Cardiovascular, Respiratory and Nervous system were examined. A complete hemogram, LFT, renal function were done. Doppler studies of renal arteries were done. OGD was done with in one day of admission.

Doppler studies were performed in patients after overnight fasting. Doppler study was done using a duplex Doppler apparatus with a color Doppler sonographer and 3.75 MHz convex transducer. The transducer was positioned below the costal margin in the dorsolateral area of the flanks. The intrarenal artery of the kidney could be easily identified by color Doppler ultrasonography.

The sampling volume of the pulsed Doppler system was placed in the intralobar artery along the border of the medullary pyramids, and the blood velocity wave form was recorded. The maximum systolic velocity, end diastolic minimum velocity, and mean velocity were determined. The Pulsatility index and resistive index were calculated according to the following formulae.

$$PI = \frac{\text{Mean Systolic velocity} - \text{End Diastolic Minimum Velocity}}{\text{Mean velocity}}$$

$$RI = \frac{\text{Mean Systolic velocity} - \text{End Diastolic Minimum Velocity}}{\text{End Diastolic Minimum Velocity}}$$

Patients were treated with salt restriction 50meq/d and diuretics after Doppler studies with combination of Spironolactone and frusemide starting with a smaller dose and increasing dose according to response.

Body weight was measured daily. Satisfactory Response was defined as mean body weight loss of two hundred grams as defined by Neven Ljubicic etal (Scandinavian journal of gastroenterology April 1998).

Mean body weight loss of less than two hundred grams with 200mg/day with an intake of spironolactone and 120mg/day of frusemide was defined as unsatisfactory response to diuretic therapy (resistant ascites).

Esophageal varices were graded according to Pacqet classification and Cirrhosis graded by Childs grading.

CHILDS GRADING OF LIVER DISEASE

	A	B	C
S. Bilirubin	<2mg	2-3mg	>3mg
S.Albumin	>3.5mg	3-3.5mg	<3mg
Ascites	None	Easily controlled	Poorly controlled

Neurological disorder	None	Minimal	Coma
Nutrition	Excellent	Good	Wasting

Child A 5-6 Child B 7-9 Child C 10-15

GRADING OF ESOPHAGEALVARICES

Grade 1: Varices are small and straight.

Grade 2: Varices are tortuous and occupying less than one third of lumen.

Grade 3: Varices occupying more than one third of the esophageal lumen.

Grade 4: Varices occluding the lumen of esophagus.

Data was entered and all the statistical analysis was done Using stastistical analysis software Epi Info 2.3.4 windows version

Normal values were taken from previous studies involving normal subjects

Normal values

RI----0.62+/- 0.05

PI----1.00+/- 0.12

RESULTS

A total of 57 subjects participated in the study. The mean age of the patients was 44, with a range from 30-75 years. Of the 57 patients, 44 were male and 13were female.

DEMOGRAPHIC PROFILE

Age	**Mean**	49
	Median	49
	Standard deviation	12.4
	Range	30 to 75
Sex	Male	44 (77%)
	Female	13 (23%)
Child	A	12 (21%)
	B	26 (46%)
	C	19 (33%)

Based on clinical and data from investigations 12 patients were categorized to Child A, 26 to child B, 19 to Child C.

HBV (35%) infection was found to be the commonest cause found in 20 patients, alcohol abuse was seen in 18 (31%) patients, HCV (17.5%) were detected in 10 patients. Other causes include BCS, PBC, AIH, unknown causes.

ETIOLOGY

ALCOHOL	18 (31%)
HBV	20(35%)
HCV	10(17.5%)
OTHERS AND COMBINED	9(15%)

Resistive index and the Pulsatility index was found to be 0.72 with a standard deviation of 0.06,1.48 with a standard deviation of 0.24 in cirrhosis patients which is higher than in normal population.

RI AND PI IN CIRRHOSIS

RI	**Mean**	0.72
	Median	0.72
	Mode	0.73
	Standard deviation	0.06
	Range	0.60to 0.85
	% normal (0.62 ± 0.05)	13 (23%)

PI	Mean	1.48
	Median	1.40
	Mode	1.40
	Standard deviation	0.29
	Range	0.99 to 2.20
	% normal (1.00 ± 0.12)	5 (9%)

Of these patients only 13(23%) patients had RI in normal range. while only 5(9%) patients have Pulsatility index in normal range. On subgroup analysis of patients in different grade of cirrhosis.

RI IN DIFFERENT GRADES

Child grading	**A (n=12)**	**B (n=26)**	**C (n=19)**
Mean	0.64	0.71	0.78
Median	0.65	0.71	0.78
Mode	0.65	0.73	0.76
Standard deviation	0.025	0.019	0.036
Range	0.60 to 0.68	0.67 to 0.73	0.71 to 0.85

% normal (0.62 ± 0.05)	11 (92%)	2 (8%)	0 (0)

Kruskal-Wallis H (equivalent to Chi square) =45.3; p< 0.001

The mean value of RI was found to be as follows.

Child A …….. 0.64 with standard deviation of 0.025.

Child B …….. 0.71 with standard deviation of 0.019.

Child C…….. 0.78 with standard deviation of 0.036.

Among those 12 patients in Childs A group it was found 11(92%) patients had RI in the normal Range. Only 2 out of 26 (8%) Grade B cirrhoses, none of patients in Child C had RI in the normal range.

Resistive index showed a significant increase With increasing severity of cirrhosis.Kruskal- Wallis H value was calculated to study the correlation between resistive index and severity of cirrhosis. It wasfoundto be 45.3 with a Pvalue< 0.0001 which is statistically significant. The mean Pulsatality index was1.15 with standard deviation of 0.086 in child A cirrhosis,1.38 with standard deviation of 0.086 in Child Cirrhosis, 1.83 with standard deviation of 0.180.

PI IN GRADES OF CIRRHOSIS

Mean	1.15	1.38	1.83
Median	1.16	1.38	1.78
Mode	1.20	1.40	1.69
Standard deviation	0.086	0.086	0.180
Range	0.99 to 1.30	1.29 to 1.55	1.60 to 1.69
% normal (1.00 ± 0.12)	5 (42%)	0 (0)	0(0)

Kruskal-Wallis H (equivalent to Chi square) =47.8; $p < 0.001$

Pulsatility index was within the normal range in 5 out of the 12 patients (42%) in Child A group while none of the 26 patients in ChildB, 19inChildC had PI in the normal range.Esophageal varices were seen in eight patients while 3 did not have varices in childA cirrhotic patients.All the 3 patients who did not have esophageal varices had a normal resistive index.

OESOPHAGEAL VARICES BY RI LEVEL

RI level	No. of varices					Total
	NO	1	2	3	4	
Within normal range	3	6	3	0	1	13
Outside normal range	0	15	22	6	1	44
Total	3	21	25	6	2	57

RI value and presence of oesophageal varices among ChildA graded cirrhosis patients (N=8) are strongly and positively correlated(correlation coefficient is 0.67)However, this observation is based on just eight patients. This suggests a positive correlation between presence of esophageal varices and resistive index.

Out of the 57 patients in this study 45 patients were treated with diuretics.40 (70%) patients responded to diuretics.while 5(9%)patients did not respond to diuretics.

RESPONSE TO DIURETICS BY RI LEVEL

RI level	Response to diuretics		Total
	Yes ; Respond to diuretics	Resistant to diuretics	
Within normal range	2	0	2
Outside normal range	38	5	43
Total	40	5	45

38 out of 40 patients who had adequate response had RI outside normal range. While only 2 patients had RI in the normal range. Among the non responder all the 5 patients RI were outside normal range.

RI level	Mean (Standard deviation)
Respond to diuretics	0.73 (0.036)
Resistant to diuretics	0.83 (0.016)

Kruskal-Wallis H = 13.2; p value=0.0003

The mean RI was 0.73(standard deviation of 0.036) and 0.83 (Standard deviation of 0.010) in diuretic responsive and non responsive group. Krushal –Wallis H value for correlation between mean RI and diuretic response was 13.2 with p value of 0.0003 which is stastically significant.

DISCUSSION

This study was carried out in a tertiary level hospital. Most of the patients are from north Tamilnadu and few from Andrapradesh. Mean age of the patients in this study was 49 +/- 12. Mean age of patients with cirrhosis in study by Joshi etal[1] was 45 which is similar to this study.

Out of 57 patients in this study 44(77%) were male and13 (23%) were female. Male female ratio is 3:1. S.kSarin etal[24] reported a similar sex distribution in their study. The causes of cirrhosis vary in different places.

The most common cause of cirrhosis in this study was Hepatitis B Virus (35%) infection followed by ethanol and HepatitisC Virus.Joshietal[1]have reported similar figure in their study HBV (30%), alcohol (20%), HCV (14%). The higher number patients in this study in alcohol group could be due to referral bias.

As all patients with History of alcohol abuse are referred from Institute of mental health for evaluation of hepatocelluar function to our hospital. Prevalence of HCV is comparable in both studies.

Marota etal [2] and Platt etal[3] were among first authors to show RI is increased in patients with nonazotemic functional renal failure in addition to other

causes like ATN, renal arterial thrombosis[14,15,16].

Renal arterial vasoconstriction is said to be the main pathophysiology in volume overload. This was ascribed to high levels of vasoconstrictors. N.Ljubicic etal[20] showed that RI is increased in cirrhosis. Further studies by Masohika Koda [19] have shown that RI also increases with progressive in grading of cirrhosis.

This study also shows a similar finding. The mean RI value is 0.72 +/- 0.06 and PI is 1.48+/-0.29 which is higher than normal values (0.57-0.67,0.88-1.12). Masohika Koda etal have also showed that this increasing value of RI is associated with increasing level of serum vasoconstrictors rennin,aldosterone,and epinephrine.This study also shows mean RI & PI to increase with increasing grade of cirrhosis.

MEAN RI & PI ARE

Grade	RI	PI
Child A	0.64 +/- 0.025	1.15 +/- 0.086
Child B	0.71 +/- 0.019	1.38 +/- 0.086
Child C	0.78 +/- 0.036	1.38 +/- 0.180

Kruskal- Wallis N value for correlation between severity of cirrhosis and RI & PI values was significant with a p value of < 0.001.

Out of the 57 patients in this study patient 45 patients were treated with diuretics. 70% responded adequately to diuretics, 9percentof patients were non responders according to definition of Ljubicic[20].The prevalence of diuretic resistant ascites is accepted to be around 10%. Gatta etal [11] have reported a prevalence of 9% .A study by Perez –Ayuso[25] also report a prevalence of 10%.

Definition used in this study is not same as International ascites club definition. Sungaila etal[10] have showed patients who do not respond to 200mg of spironolactone, and 120mg of frusemide are unlikely to respond to dose escalation. Ljubicic has based his definition on this study .Further studies are needed to know if patients with inadequate response represent the classical diuretic resistant ascites.

This study also shows that a high value of RI is noninvasive predictor of

inadequate response to ascites.However this observation is based on a small cohort. Studies involving larger sample is needed to confirm this finding.

Analysis of ChildA cirrhosis subgroup shows that an elevated RI value is seen in patients with esophageal varices. Agostino colli etal [21] have reported this association in their study. This is an important observation as this indicates renal vasoconstriction precede development of ascites in cases of portal hypertension .RI could also correlate with portal hypertension.

Levy etal [26] and Schrier[27] etal havelso reported an similar observation in their studies

CONCLUSION

1. Renal Resistive index and pulsatality index are abnormal in most of the patients with cirrhosis.

2. Renal Resistive index and the pulsalility index are increased even in patients with normal renal function tests.

3. Renal Resistive index and pulsatality index show a significant and a positive correlation with increasing grade of cirrhosis.

4. Renal Resistive index is a invasive predictor of response to diuretic treatment of ascites in cirrhosis.

5. A high level of RI correlates with presence of esophageal varices.

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PROFOMA

Name of the patient:

Address:

Age/ sex:

Complaints:

a)Abdominal distention.

b) Leg swelling.

c) Oliguria.

d) Jaundice.

e) Breathlessness.

f) Hematemesis & malena

g) Alcohol use

h) drug intake

Past history:

H/O renal disease

H/O malignancy

H/O DM/ HT/ IHD/ Malignancy.

GENERAL EXAMINATION:

Consiousness	vitals/ body weight
Nourishment	signs of liver cell dysfunction.
Febrile	Evidence of malnutrition
Pallor and icterus	Lymph nodes
Pedal edema	Asterixsis

Abdominal examination

Hepatomagaly	Spleenomegaly
Ascites	Abdominal veins

Others system:

CNS:

RS:

CVS

LABORATORY INVESTIGATIONS

Complete hemogram

Liver function test:

S.bilirubin

SGOT

SGPT

ALP

S.Proteins

Albumin

Globulin

Ultrasonogram abdomen & doppler

Endoscopy

Response to diuretics