A Non Invasive Evaluation Of Variability Of Intrarenal Blood Flow At Rest And During Exercise
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Abstract:
Under normal conditions, renal blood flow is controlled by intrinsic factors and factors include an auto regulatory mechanism, intrarenal renin-angiotensin mechanism and kinins. The critical extrinsic factors include the sympathetic nervous system (SNS) angiotensin II, dopamine, nitric oxide, ADH and ANP. These multiple factors work in concert to sustain renal blood flow and glomerular filtration regardless of wide variations in systemic arterial B.P.

This investigation is devoted to assess the variability of intrarenal arterial blood flow at different regions of the kidney at rest and during dynamic exercise. The available Studies on this subject are few, conflicting and are adopting static exercise. The study is conducted on 10 male healthy individuals of age ranging between 18-30 years. The interlobar intrarenal arteries spectral parameters (PSV,MDV, R, and VTI) at upper pole, mid pole and lower pole are obtained at rest in supine and upright positions and during performing supine exercise. A color Doppler U/S Siemens versa plus equipment with 2.5 MHz phased array probe or 3.5 MHz convex probe and a bicycle ergometer(E 315) to perform supine exercise were utilized for this purpose. It was shown that: 1-The over all intrarenal blood flow is significantly higher in supine position than that in upright position. 2-The intrarenal blood flow at mid pole is significantly higher than that of lower and upper poles. 3-There is no significant difference of intrarenal blood flow between the upper and lower poles. 4-There is significant decrease of over all intrarenal arterial blood flow during dynamic exercise; it is mainly the diastolic flow which is decreased. It was concluded that this
technique would afford an indirect approach to study the renal artery blood flow. Further, this study would help to stand as a valuable method to assess renal perfusion. Moreover, it stands as an indirect method to assess renal artery stenosis before and after surgical revascularization.

Introduction:

Because of the complexity of renal blood flow control and its multifactorial regulatory mechanisms, it seems feasible to review some of the physiologic and historical aspects as these are closely related to the present study:

Under normal conditions, the kidney receives the highest blood flow per gram of organ weight in the body at 1 liter/min via the renal arteries. These arteries branch into segmental arteries which subdivide into interlobar arteries. Each interlobar artery penetrates the kidney through a column of Bertin, before reaching the cortical surface divides into arc-shaped arcuate arteries, which run parallel to the surface. Branching from each interlobular artery are many arterioles to form the afferent arterioles. Each afferent arteriole gives rise to a tuft of capillaries within Bowman’s capsule that combine to form the efferent arteriole which is considered as resistance vessels. These arterioles possess smooth muscle and therefore, can vary their level of vasoconstriction.

Renal function is dependent upon generous blood flow to the kidneys and is dependent on systemic blood pressure. However, actual renal perfusion, and hence adequate glomerular perfusion, is further dependent on intra-renal vascular resistance. Moreover, autoregulatory mechanisms, through changes in vascular resistance, ensure that over a wide range of perfusion pressures renal blood flow remains stable and glomerular filtration can be maintained. These autoregulatory mechanisms are primarily local and intrinsic but systemic inputs also affect renal blood flow.

The intrinsic factors include intrarenal rennin-angiotensin mechanism, eicosanoids, and kinins. Critical extrinsic factors include the Sympathetic Nervous System (SNS), angiotensin II, antidiuretic hormone (ADH), dopamine, and histamine. Endothelin, nitric oxide (NO), and atrial natriuretic peptide (ANP) also play important roles in altering renal hemodynamics. These multiple factors work in concert to sustain glomerular filtration, despite the wide variation in systemic blood pressure. The Intrinsic autoregulatory mechanism means that the intrarenal system, maintains a consistent RBF despite mean arterial pressure (MAP) fluctuations from about 80-180 mmHg, but becomes dysfunctional when the MAP is outside this range.

There are two mechanisms believed to be involved in this autoregulatory phenomena: the myogenic and the tubuloglomerular feedback (TGF) mechanisms. The myogenic mechanism is based on the function of baroreceptors (stretch receptors) in the afferent arterioles: When the MAP increases, these receptors respond to the increased vascular wall tension or stretch and cause afferent arteriolar constriction. This constriction prevents transmission of the elevated arterial pressure to the glomerulus, thus maintaining a normal GFR. There appears to be no effect on the efferent arteriole.

The TGF mechanism relates to the function of the macula densa and juxta-glomerular cells. In conditions that increase RBF and, thus, GFR, there is an increased delivery of sodium chloride (NaCl) to the macula densa cells in the distal nephron. When these cells
detect this increased NaCl load, they mediate vasoconstriction of the afferent arteriole via an unknown messenger substance, resulting in a decrease in the glomerular blood flow, a decrease in perfusion and a return of the GFR toward normal. However, Renin-Angiotensin Mechanism is regarded as a critical regulator of intrarenal blood flow that is triggered by internal and external stimuli. It is more important than any other regulatory mechanism during episodes of hypotension when renal ischemia occurs.

Several sophisticated techniques were performed to assess and quantify total RBF at rest and during exercise. Among these: Invasive percutaneous Intravascular Doppler wire was utilized to measure single-kidney measurements of blood velocity and to document renal arterial diameter to enable calculation of RBF. However, in larger or more tortuous tubes and for flow rates >200 mL/min (which are common in the renal artery), this technique may underestimate blood flow. Such a pitfall was attributed to suboptimal positioning and wire instability or because of deformed flow profiles.

Other diverse costly noninvasive techniques were used to quantify intra renal haemodynamics Including Electron beam Computerized Tomography “EBCT”, MRI and Xenon 133. The Xenon 133 (133Xe) washout technique is based on evaluation of the excretion profile of an externally administered indicator. This method has been very useful for assessment of RBF and its response to a wide spectrum of vasodilators. However, using this technique, it was observed a blunted increase in RBF in response to graded doses of acetylcholine and dopamine in patients with parenchymal disease but observed a potentiate response in patients with increased basal renal vascular resistance (RVR) or mild essential hypertension and no structural damage.

In a study performed on animal, the distribution of renal and intrarenal blood flow (IRBF) was investigated in swine at rest and during severe exercise using tracer microspheres. In this study, it was shown that renal artery blood flow is significantly reduced in pigs with exercise. Steady-state exercise reduced flow to about 66% of control and severe exercise reduced renal flow to 30% of control. IRBF was unchanged throughout.

Similar results obtained in baboons during mild dynamic leg exercise. In this study total renal blood flow was measured invasively by an electromagnetic flow transducer through the left renal artery.

In an indirect assessment of RBF during exercise the renal tubular function was investigated in horses during sub maximal exercise. In this study it was shown that exercise significantly increased plasma osmolality, plasma [K+], urine flow, Na+ excretion and K+ excretion. These changes are accompanied by increases in plasma atrial natriuretic peptide (ANP), plasma renin activity, plasma aldosterone concentration and Vasopressin concentration.

In another study Performed on human, the renal Cortical Blood Flow was investigated during Static Exercise. In this study renal cortical blood flow was measured using dynamic positron emission tomography (PET) during graded handgrip exercise, post handgrip circulatory arrest, and after administration of intra-arterial adenosine to clarify the mechanisms controlling renal blood flow during static exercise. It was observed that renal cortical blood flow decreases and renal cortical vascular resistance increases in response to graded hand grip exercise. Also, it was demonstrated that exogenous adenosine activates the muscle metaboreflex producing reflex renal vasoconstriction and decreased renal blood
flow. A production of endogenous adenosine during ischemic exercise was implicated as a potential activator of the muscle metaboreflex during ischemic handgrip exercise.

In an invasive study, in anaesthetized rabbits, using laser-Doppler flowmetry, it was shown a decrease of cortico-medullary blood flow and GFR in response to graded renal sympathetic nerves stimulation.

A noninvasive Doppler technique was utilized to study intrarenal blood flow: The effect of aging on renal blood flow velocity during static exercise (Hand grip) was investigated. It was found that Static exercise-induced renal vasoconstriction which is enhanced with aging. Standardization of the Resistant index “RI” in the interlobar arteries in different regions of the kidney, and its relation to secretion of Renin and Aldosterone, also studied using the same technique. In another study factors that affect renal Doppler wave form were assessed. However, in these studies, no attempt was made to quantify renal blood flow.

Methods:

The present study was conducted on 10 healthy young male subjects of age ranging between 18-32 years old. The intrarenal blood flow was studied using color Doppler U/S Siemens versa plus equipment with 2.5 MHz phased array probe or 3.5 MHz convex probe. For this purpose segmental interlobar renal arteries Fig 1) was interrogated by first color flow assignment and then by power Doppler technique by placing the Doppler sample volume cursor in the interlobar segmental artery under study, at angle set at 0°- 35°; and the sample volume used is adjusted at 3mm.(5,7)

Care was taken not to exert much pressure on the kidney when insonating renal arteries as this may hamper the flow and may affect Doppler parameters. The right kidney was utilized in this investigation for technical purposes, for its easy approach; as it lies on the same side of the ultrasound machine. Two protocols were used:

First: The variability of intrarenal blood flow at different regions of the kidney was first assessed at rest when changing position from supine to upright. This was achieved by obtaining intrarenal arteries wave form spectral parameters: The Resistant index (RI), Peaked Systolic Velocity (PSV), Mean Diastolic Velocity (MD) and Velocity Time Integral (VTI) at mid pole, upper pole and lower pole in supine position. The same mentioned parameters were obtained when changing to upright position. Insonation of intrarenal arteries of the right kidney was performed through the right upper abdomen by asking the patient to hold breath following deep inspiration, as long as he can. Care was taken to obtain the highest systolic upstroke and a good spectral wave form. Doppler derived of the above cited parameters in supine and upright positions were then statistically analyzed and correlated.

The second protocol was to study variability of renal blood flow during mild to moderate exercise: Two methods of exercise were used. In the first method the subject lies prone and asked to perform fast repetitive flexion and extension leg movements for 5 min, while the interlobar intrarenal arteries were insonated posteriorly. The second method “adopted in this study” was by using friction-braked bicycle ergo meter (E 315; Fig2). The bicycle was mounted on the examination table and the subject who lies supine was instructed to perform cycling for 3min. at 50w work load. The renal arteries were insonated anteriorly...
from the right upper abdomen. Care was taken not to exert too much compression on the kidney with the transducer while insonating the segmental arteries,\(^{(5)}\).
The obtained spectral wave form parameters (RI, PSV, MDV and VTI) during supine exercise were then statistically analyzed and correlated with the parameters obtained at rest.

The resistance (force in Kilopond “kp”) against which the subject performs cycling can be adjusted at a constant level by manipulating the resistant knob fitted on the bicycle ergometer. The work load output can be kept constant and is automatically displayed on the attached screen of the ergometer. It also displays speed, distance, time, heart rate and Calories. However, if drifting occurs then the work load can be worked out manually using the following biophysical well established Data (18):

Since Force is defined as mass multiplied by acceleration, so the units are $kG\cdot M/Sec^2$. The Newton (N) is used as a unit of force in honor of the English physicist, Isaac Newton (1642 - 1727).

$1\ kG\cdot M/Sec^2 = 1\ N$

The pound weight was replaced by a one kilogram mass. The replacement force, called a kilopond (kP), is the force generated when the kilogram mass is accelerated by earth’s normal gravity. This force can be converted to Newtons.

$1\ kP = 9.8\ N$

Work is force applied over a distance, or force multiplied by distance. The units are $N\cdot M$. The Joule (J) is used as a unit of work in honor of the Englishman James Prescott Joule (1818 - 1889), one of the founders of thermodynamics.

When the English kilopond is used to describe work, the units are kilopond-meter (kP·M). Sometimes the kilopond-meter is referred to as a kilogram-meter (kG·M).

$kP\cdot M = 9.8\ J$

Work is one of the forms of energy. Another form of energy is the calorie (Cal). A calorie is the amount of heat needed to raise the temperature of one gram of water one degree C (from 14.5° C to 15.5° C).

$1\ Cal = 4.19\ J$
Power is work divided by time. The unit is J/Sec. The Watt (W) is used as a unit of power in honor of James Watt (1736 - 1819) the Scottish inventor of a practical steam engine.

1 J/Sec = 1 W

Returning to the old English system, we come to the units for power. The units are kP·M/Min.

1 kP·M/Min = 0.163 W

These units are often used to describe the intensity of exercise.

A useful conversion is Watts to Cal/Min.

14.3 Cal/Min = 1 W

As mentioned earlier, the calories are displayed on the ergometer screen and therefore the work load can be calculated accordingly.

In this study, VTI (which means integrating the area under the velocity curve over time by simply measuring the velocities at each point in time and summing all these velocities) is utilized to investigate the degree of change in RBF when changing posture and during exercise. The VTI can be measured either manually or via velocity integration software built in most new generation colored Doppler equipment. The VTI also termed stroke distance which indicates the distance that blood travels during one flow period. Knowing the VTI and the diameter of the insonated segment of the intrarenal artery would help in estimation of regional intrarenal blood flow.

Results:

Spectral wave form configuration: Doppler derived wave forms of segmental arteries, at different regions of the kidney are presented in Fig (2). The normal spectral wave form obtained at rest is pulsatile, diphasic, and characterized by sharp rapid upstroke, having double systolic peak, and of high diastolic flow. No reversal element observed.

![Upper pole](image1)

![Mid pole](image2)

![Lower pole](image3)

Fig (2)
In general, the wave form obtained in supine or upright position, at mid pole was found to have higher peaked systolic velocity (PSV) and mean diastolic velocity (MDV) than those obtained at upper and lower poles.

Doppler derived parameters RI, PSV, MDV, VTI of the blood flow obtained at rest, at different regions of the kidney when changing posture from supine to upright position are shown in table 1.

Table (1)
The Resistive indices (RI) of the flow obtained at the upper pole, mid pole and lower pole in supine and upright positions are presented in Fig. (3). At upper pole, there was borderline significant increase of RI when changing posture from supine to upright position, whereas no significant change in RI observed in mid pole and lower pole.

![Fig. (3): Resistive Indices “RI” of the flow at different regions of the kidney when changing posture from supine to upright position](image)

The peaked systolic velocities (PSV) of the flow obtained at the upper pole, mid pole and lower pole in supine and upright positions are shown in Fig. (4). There was significant decrease of PSV of the flow in all three regions of the kidney in response to change of posture from supine to upright position. This decrease was found to be more evident in mid pole and upper poles.

![Fig. (4): PSV of the flow (cm/sec) at different regions of the kidney when changing posture from supine to upright position](image)
The mean diastolic velocities (MDV) of the flow obtained at the upper pole, mid pole and lower pole in supine and upright positions are shown in Fig. 5). There was a significant decrease of the MDV of the flow at upper and mid pole to change of posture from supine to upright position. No significant change of the flow at the lower pole.

Fig (5). MDV of the flow (cm/sec) at different regions of the kidney when changing posture from supine to upright position.

The Velocities Time Integral (VTI) of the flow (cm) obtained at the upper pole, mid pole and lower pole in supine and upright positions are shown in Fig. (6). There was significant decrease of VTI of the flow at mid pole when changing posture from supine to upright position. No significant change in VTI observed at upper and lower poles.

Fig (6): VTI of the flow (cm) at different regions of the kidney when changing posture from supine to upright position.

The above Doppler derived parameters obtained at different regions of the kidney were then correlated in both supine and upright positions (Fig 7). It was found that the PSV, MDV and VTI obtained at mid pole were significantly higher than those obtained at upper pole.
Results of Doppler derived parameters of Intrarenal Blood Flow in supine exercise:
For this purpose the intrarenal arteries in the middle pole of the right kidney were utilized to perform Doppler study, for technical reasons. When performing exercise on supine position, abnormal bizarre shaped Doppler wave form spectra obtained as shown in fig.(8)

Table (2) shows the mean and range of RI, PSV, MDV, VTI at rest and during supine exercise, as well as, the mean and range of difference and the P values.
In supine exercise, the peaked systolic velocity (PSV) was found to decrease or increase with border line significance (p: 0.1), but the mean diastolic velocity (MDV) was found consistently and significantly decreased or some times absent (P: <0.001), as shown in Fig 9.

The velocity time integral (VTI) of renal blood flow was found significantly decreased (P<0.001) and the resistant index (RI) significantly increased (P<0.05) when performing exercise on supine position (Fig 10). These changes in renal blood flow as a result of exercise were of very rapid onset and offset; it takes only few seconds to result and to disappear when stopping exercise (Personal observation).
Discussion:

In the present study more information was provided on the normal configuration and characteristics of Doppler spectra of intra renal blood flow at different regions of the kidney. There is rapid systolic upswing and prolonged gradual diastolic decay. The systolic element is usually very rapid and of double peak; the first peak is noted to be higher than the second one. These Doppler spectral findings of intra renal blood flow resemble the wave form obtained from the renal artery from its origin from the abdominal aorta as shown in Fig. 11 A&B, as an example: In Fig 11A. The left renal artery was insonated through a Trans lumbar approach from its origin from the aorta. In Fig 11B, the right renal artery was insonated from anterior abdominal approach.
This fact is of paramount importance as intrarenal artery Doppler may be used in many circumstances as a “surrogate” to assess main renal arteries blood flow when there is failure of insonation of these arteries from their origin from the abdominal aorta.

Further more, the obtained results of Doppler derived parameters would serve as a reference for the future studies:

The RI is one of the Doppler parameters that provides information about arterial impedance. The resistant indices of intrarenal blood flow obtained at rest were of a range of 0.51 – 0.70. This finding is rather consistent with previous studies.\(^{(5,7,27)}\) In the present study no RI below 50 or above 70 obtained. The result of slight increase of RI in the upper pole, when changing from supine to upright position “border line significance” may be attributed to the gravitational effect. However, it is to be pointed out that RI may be affected by heart rate: The higher heart rate, the higher end diastolic velocity measured before the next heart beat follows and vice versa.\(^{(5)}\)

At rest, there was significant increase in overall intrarenal blood flow in supine position than that obtained when changing posture to upright position. This finding may be explained as a result of increased venous return and hence cardiac output in supine position.

At mid pole there were significantly higher PSV & MDV, in both supine and upright positions, than those obtained at upper and lower poles. This may be explained as due to the larger segmental branch supplying the midpole which appears to lie in direct continuity with the distal portion of the main renal artery fig.1), causing an increase of the blood volume and flow. However, no significant change to borderline significant change of RBF RI obtained in all regions, when changing posture from supine to upright position. This result may be attributed to the auto regulatory mechanism of intrarenal arterioles and perhaps would further backup the myogenic theory.\(^{(14,29)}\)

In this investigation, the Doppler derived VTI was utilized to study regional renal blood flow. So far, in the available literatures, no studies have adopted this technique to estimate renal blood flow. In fact many investigators used the VTI to estimate the cardiac output by calculating stroke volume from the Doppler spectra of the transaortic flow.\(^{(10)}\) An example to estimate the VTI of a segmental artery at midpole is shown below (Fig 12); it represents
the hatched area of the Doppler wave form T0 to T1. The area under velocity curve is measured as the sum of velocities at each point integrated over time. The result is a measure of distance “in cm”.

Fig. (12)

Knowing the diameter of the segmental artery and its RI, then intrarenal regional blood flow can be estimated using the formula: \( D^2 \times 0.785 \times \text{VTI} \) (10). Conventionally, a high vascular resistance impedes the flow and is different in different regions of the kidney, thus the flow volume should be further normalized with respect to RI: It follows:

\[
\frac{D^2 \times 0.785 \times \text{VTI}}{\text{RI}} \quad (10.2)
\]

Global renal blood flow can be estimated using the same technique, as the distal portion of the renal artery is easily accessible when insonated posteriorly, from the flanks. Thus, this non-invasive technique would provide a safe, cheap and rather easy method to estimate RBF, in contrast to the sophisticated techniques cited earlier.

When interrogating intrarenal arteries during performing supine submaximal exercise:

The finding of highly significant reduction of flow is in accordance with previous studies (16,17,20,23,27). However in these studies, no comment was made on the contribution of systolic or diastolic element in the flow change during exercise. Furthermore, in some of these studies static exercise was adopted (16) and most of the studies were performed on animal using costly invasive techniques (23,27).

In the present study, the diastolic component of the flow was found to decrease profoundly, in contrast to the systolic flow which was rather unchanged significantly. This finding would beautifully explain the importance of the contribution of the nervous control of RBF: On exercise, the increased overall sympathetic nerves activity and of the renal sympathetic nerves innervating the afferent arterioles would cause constriction of these arterioles resulting in decreasing of the flow despite the increased cardiac output during performing exercise.

Further support to the sympathetic control comes from the finding of rapid onset of the change of Doppler spectral wave form on exercise and rapid return to normal pattern when
the exercise aborted. Moreover, the RI significantly increased during exercise due to profound decrease of the diastolic flow, since the flow is pulsatile and RI is derived as
\[ \text{peaked systolic velocity} - \text{end-diastolic velocity} / \text{peaked systolic velocity}. \]

In the present investigation, the flow volume change during exercise can be estimated via VTI. A note should be made that in pulsatile flow, as in case of renal arterial flow, it is empirical to conclude a flow volume increase from increased PSV alone, the wave form may be shallow and the diastolic flow may be of short runoff. From this comes the fact of application of VTI to precisely assess any change of RBF. The obtained results, utilizing the VTI parameter, show a clear and definite decrease of RBF despite the increase in PSV on some occasions during exercise (Fig.9).

Several studies,\(^{(7,26,29)}\) adopted the RI and wave form configuration of intrarenal arteries to assess renal artery stenosis before and after surgical intervention, or to investigate the occurrence of renal parenchymal damage. Fig 13 A&B shows an example of the difference in wave form configuration:

Fig. 13A shows a normal intra renal artery flow at mid pole obtained in the present study, and hence a normal renal artery flow: A sharp, rapid and high upstroke are evident. Fig. 13B shows doming of the systolic upswing with prolonged acceleration time indicating diminished intra renal blood flow at mid pole due to renal artery stenosis (RAS).

The present results would form a “gold” slandered for such investigations. Moreover, using the VTI parameter would add further help to assess none invasively RAS before and after surgery and the flow volume change on exercise. Also VTI parameter can be adopted to study the effect of certain drugs on flow volume changes in renal artery or intrarenal arteries...

Fig. (13)

(A) Normal intra renal flow                              (B) Intra renal flow of renal artery stenosis

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