MEASUREMENT OF RENAL FUNCTION USING PERFUSION STUDY BY MULTI DETECTOR COMPUTED TOMOGRAPHY

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Introduction: Renal function is an indication of the state of the kidney and its role in renal physiology. Accurate measurement of total or differential renal function plays an important role in the clinical management of various renal diseases. The Glomerular filtration rate (GFR) has been shown to be a reliable index to physiologic renal function (Shannon JA *et al*). Tissue perfusion can be estimated by calculating time – attenuation curve from dynamic CT acquisitions also known as CT perfusion (CTP) study (K A Miles *et al.,* 1991). Currently, Perfusion CT has also been applied in a range of additional clinical areas. This study investigates the perfusion parameters in evaluation of the renal function using MDCT.

Objectives: This study aims to evaluate the renal perfusion and to compare with estimated glomerular filtration rate (eGFR) by using multi detector computed tomography.

Patients and Methods: Thirty two patients who fulfilled the inclusion criterias were enrolled in this study which was carried out from November 2009 till October 2010, in Department of Radiology, Hospital Universiti Sains Malaysia. Blood for plasma renal function test which includes the urea and creatinine was taken prior to the CT examination. All the subjects underwent plain CT scanning of the abdomen using a 64-multidetector CT SIEMENS SOMATOM Definition AS followed by perfusion scanning done at the level of renal hilum. All images were transferred to a SIEMENS SOMATOM Definition AS workstation analysis. The data was analyze using time-density curve. The cursor was set on the aorta at the renal hilum level. The region of interest (ROI) was located at the cortex, medulla and whole kidney, away from the vessels. The average tissue attenuation using a manually drawn ROI on each image was automatically calculated and perfusions parameters which include blood flow (BF), blood volume (BV), mean transit time (MTT), time to peak (TTP) and maximal intensity phase (MIP) value were measured. Pearson product – moment correlation coefficients were calculated to assess relationship between the BF, BV, MTT, TTP as well as MIP with eGFR.

Results: Pearson analysis revealed the significant inverse correlation between eGFR and TTP in cortex, medulla and whole kidney bilaterally ($p<0.05$). However, there is no significant correlation found between BF, BV, MTT and MIP with eGFR ($p>0.05$).

Conclusions: This study showed that time to peak (TTP) is a potential parameter to estimate the GFR, and multidetector computed tomography (MDCT) is a useful tool in estimating the regional renal function in non invasive way.

PM Dr Mohd Ezane Aziz: Supervisor

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by :

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ABBREVIATIONS

BF	Blood Flow
BV	Blood Volume
CKD	Chronic Kidney Disease
CTP	CT Perfusion
eCcr	Estimated Creatinine Clearance Rate
eGFR	Estmated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
HU	Hounsfield Unit
MDCT	Multidetector Computed Tomography
MDRD	Modification of Diet in Kidney Disease
MIP	Maximal Intensity Projection
MTT	Mean Transit Time
MRI	Magnetic Resonance Imaging
ROI	Region of Interest
TAC	Time Attenuation Curve
TTP	Time to Peak

ABSTRAK

TAJUK

Pengukuran fungsi ginjal menggunakan kajian perfusi oleh Multidetector Computed Tomography (MDCT).

PENGENALAN

Fungsi ginjal merupakan penunjuk dari keadaan ginjal dan peranannya dalam fisiologi ginjal. Pengukuran tepat dari jumplah keseluruhan atau perbezaan fungsi ginjal memainkan peranan penting dalam pengurusan klinikal pelbagai penyakit ginjal. Kadar penapisan glomerular (GFR) telah terbukti menjadi indeks yang boleh dipercayai untuk fungsi fisiologi ginjal (Shannon JA et al). Perfusi tisu boleh dianggarkan dengan kurva atenuasi masa (time attenuation curve) (KA Miles et al, 1991) dari pengambilalihan CT dinamik, juga dikenali kajian perfusi CT (CTP). Pada masa sekarang, CTP juga telah dilaksanakan dalam pelbagai bidang klinikal. Kajian ini mengkaji perfusi dalam penilaian fungsi ginjal menggunakan MDCT.

TUJUAN

Penyelidikan ini bertujuan untuk menilai perfusi ginjal dan membandingkannya dengan estimasi kadar filtrasi glomerular (eGFR) dengan menggunakan MDCT.

BAHAN DAN PESAKIT

Tiga puluh dua pesakit yang memenuhi criteria dimasukkan dalam kajian yang dilakukan dari November 2009 hingga Oktober 2010, di Jabatan Radiologi, Hospital Universiti Sains Malaysia. Darah untuk ujian fungsi ginjal yang meliputi urea dan kreatinin diambil sebelum pemeriksaan CT. Semua subjek menjalani CT scan bahagian abdomen menggunakan 64-MDCT jenama SIEMENS SOMATOM Definition AS diikuti oleh perfusi imbasan yang dilakukan pada bahagian hilus ginjal. Semua imej telah dialihkan kepada SIEMENS SOMATOM Definition AS workstation analysis. Data dianalisis menggunakan graf kurva atenuasi masa (time attenuation curve). Kursor ditetapkan pada aorta di peringkat hilus ginjal. Range of interest (ROI) terletak di korteks, medula dan seluruh ginjal, jauh dari salur darah. Anggaran atenuasi tisu Otomatik dibuat dengan melukis ROI secara manual dan perfusions parameter yang terdiri daripada aliran darah (BF), volume darah (BV), anggaran masa transit (MTT), masa ke puncak (TTP) dan fasa intensitas maksimum (MIP) diukur. Pearson product-moment correlation coeffients dikira untuk menilai hubungan antara BF, BV, TTP, MTT serta MIP dengan eGFR.

KEPUTUSAN

Pearson analisis menunjukkan bahawa korelasi antara eGFR dan penurunan TTP secara statistik adalah signifikan dalam korteks, medula dan seluruh ginjal ($p<0.05$).

Namun tidak ada hubungan yang signifikan ditemui di antara BF, BV, MTT dan MIP dengan eGFR ($P>0.05$).

KESIMPULAN

Kajian ini menunjukkan bahawa TTP merupakan parameter yang berpotensi untuk menganggarkan GFR, dan MDCT adalah alat yang berguna dalam mengestimasi fungsi ginjal secara tidak invasif.

ABSTRACT

TOPICS

Measurement of renal function using perfusion study by Multidectector Computed Tomography (MDCT).

INTRODUCTION

Renal function is an indication of the state of the kidney and its role in renal physiology. Accurate measurement of total or differential renal function plays an important role in the clinical management of various renal diseases. The Glomerular filtration rate (GFR) has been shown to be a reliable index to physiologic renal function (Shannon JA *et al*). Tissue perfusion can be estimated by calculating time – attenuation curve from dynamic CT acquisitions also known as CT perfusion (CTP) study (K A Miles *et al.,* 1991). Currently, Perfusion CT has also been applied in a range of additional clinical areas. This study investigates the perfusion parameters in evaluation of the renal function using MDCT.

OBJECTIVE

This study aims to evaluate the renal perfusion and to compare with estimated glomerular filtration rate (eGFR) by using multi detector computed tomography.

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Thirty two patients who fulfilled the inclusion criterias were enrolled in this study which was carried out from November 2009 till October 2010, in Department of

Radiology, Hospital Universiti Sains Malaysia. Blood for plasma renal function test which includes the urea and creatinine was taken prior to the CT examination. All the subjects underwent plain CT scanning of the abdomen using a 64-multidetector CT SIEMENS SOMATOM Definition AS followed by perfusion scanning done at the level of renal hilum. All images were transferred to a SIEMENS SOMATOM Definition AS workstation analysis. The data was analyze using time-density curve. The cursor was set on the aorta at the renal hilum level. The region of interest (ROI) was located at the cortex, medulla and whole kidney, away from the vessels. The average tissue attenuation using a manually drawn ROI on each image was automatically calculated and perfusions parameters which include blood flow (BF), blood volume (BV), mean transit time (MTT), time to peak (TTP) and maximal intensity phase (MIP) value were measured. Pearson product – moment correlation coefficients were calculated to assess relationship between the BF, BV, MTT, TTP as well as MIP with eGFR.

RESULT

Pearson analysis revealed the significant inverse correlation between eGFR and TTP in cortex, medulla and whole kidney bilaterally ($p<0.05$). However, there is no significant correlation found between BF, BV, MTT and MIP with eGFR ($p>0.05$).

CONCLUSION

This study showed that time to peak (TTP) is a potential parameter to estimate the GFR, and multidetector computed tomography (MDCT) is a useful tool in estimating the regional renal function in non invasive way.

1.0 INTRODUCTION

In nephrology, renal function is an indication of the state of the kidney and its role in renal physiology. It is important in regulating the water and electrolyte content of the body, retention of substances vital to the body such as protein and glucose, maintenance of acid/base balance, excretion of waste products, water soluble substances and drugs as well as endocrine function. Accurate measurement of total or differential renal function plays an important role in the clinical management of various renal diseases.

The Glomerular filtration rate (GFR) has been shown to be a reliable index to physiologic renal function (Shannon JA *et al*). Accurate determination of GFR requires the use of a substance that is freely filtered by the glomeruli and is neither secreted nor reabsorbed by the renal tubules. There are several different techniques used to calculate or estimate the glomerular filtration rate.

Clearance of inulin, a fructose polysaccharide is the gold standard for estimating GFR (Richards AN *et al*) since inulin is neither reabsorbed nor secreted by the kidney after glomerular filtration, its rate of excretion is directly proportional to the rate of filtration of water and solutes across the glomerular filter. However, the inulin clearance

method requires constant infusion of inulin and accurate timed collection of blood and urine samples.

Measuring clearance of creatinin, an endogenous substance, instead of inulin obviates the problems of constant infusion and is more practical in clinical setting. However, the creatinin clearance method still requires timed urine collection and even catheterization to evaluate total or differential renal function (Delpassand *et al.*, 2000).

More recently, calculating estimated GFR (eGFR) using an empirical mathematical formula has been encouraged. The most commonly used formula is the '4-variable Modification of Diet in Renal Disease (MDRD)' which estimates GFR using four variables; serum creatinine, age, race and gender .

Many studies in the literature have aimed to replace traditional urinary clearance methods to determine GFR with simpler and more accurate techniques. Many investigators have described quantitative nuclear medicine procedures to evaluate renal clearance that fulfill this objective. The two methods most commonly used include injection of a radiotracer followed by measurement of tracer plasma clearance (in vitro) or renal uptake of the tracer by gamma camera (in vivo) (Delpassand *et al.*, 2000). Although in vitro methods to estimate the GFR have been shown to be reliable and accurate, they have several disadvantages. Their routine use in clinical practice substantially increases the work required of the technical staff.

In vitro methods also require patients to wait as long as 4 hours and multiple manipulations in the labarotory. The site of injection must be imaged routinely to rule out paravenous injection (Delpassand *et al.,* 2000). Routine quality-control testing of the DTPA after reconstitution is essential, because an increase in protein binding of the DTPA complex after the injection can introduce a substantial error in the estimation of GFR when blood sampling is obtained after three or four hours after injection (Russel CD *et al.,* 1983). In addition, only total GFR and not differential GFR can be calculated with in vitro methods (Delpassand *et al.,* 2000).

Tissue perfusion can be estimated on the segmental basis by calculating time – attenuation curves from dynamic CT acquisitions (Miles *et al.,* 1991), also known as CT perfusion (CTP) study. Currently, the major clinical applications of perfusion CT are in acute stroke and oncology (Miles *et al.,* 2003). Perfusion CT has also been applied in a range of additional clinical areas. In hepatology, perfusion CT has been used to evaluate hepatic cirrhosis and liver allographs (K A Miles *et al.,* 1991). Cirrhosis is associated with increased arterial perfusion and decreased portal perfusion, with the degree of perfusion change reflecting the severity of liver damage.

Within the kidney, not only can CT measure the alterations of glomerular filtration (Miles *et al,* 1999), it has also been used to demonstrate reduced renal perfusion in hypertension, renal artery stenosis, renal obstruction and cyclosporin

toxicity (Miles *et al.,* 1989). To date, there is no published study in the English literature to evaluate the use of CTP in assessment of renal function in human. CTP can provide quantitative data because of linear relationship between CT value and volume concentration as well as easy acquisition of an arterial input function, which is necessary for deconvolution analysis. The source of images of CTP have high spatial resolution therefore less susceptible to artifarcts (M. Sasaki *et al, 2006*).

In this preliminary prospective study, the researcher tried to investigate the renal perfusion parameters changes with renal function using Multi-detector Computed Tomography (MDCT).

2.0 LITERATURE REVIEW

2.1 Renal Anatomy and Physiology

The renal parenchyma is divided into superficial cortex and deep medulla (figure 2.1a). Nephrons, the urine-producing functional structures, span the cortex and medulla. The cortex is the outer part of the kidney containing most of the nephrons. The inner part is the medulla, containing the specialized nephrons in juxta-medullary region, immediately next to medulla. These nephrons have a greater concentrating ability (P. Stewart, 1998). The nephron is made up of a glomerulus and its tubule. The initial filtering portion of a nephron is the renal corpuscle, located in the cortex, which is followed by a renal tubule that passes from the cortex deep into the medullary pyramids. Part of renal cortex, a medullary ray is collection of renal tubules that drain into single collecting ducts. The tubule is made up of a number of sections, the proximal tubule, the medullary loop (loop of Henle), and the distal tubule which finally empties into the collecting duct. Urine is formed as a result of three phase processes namely simple filtration, selective and passive reabsorption and lastly excretion (P. Stewart, 1998).

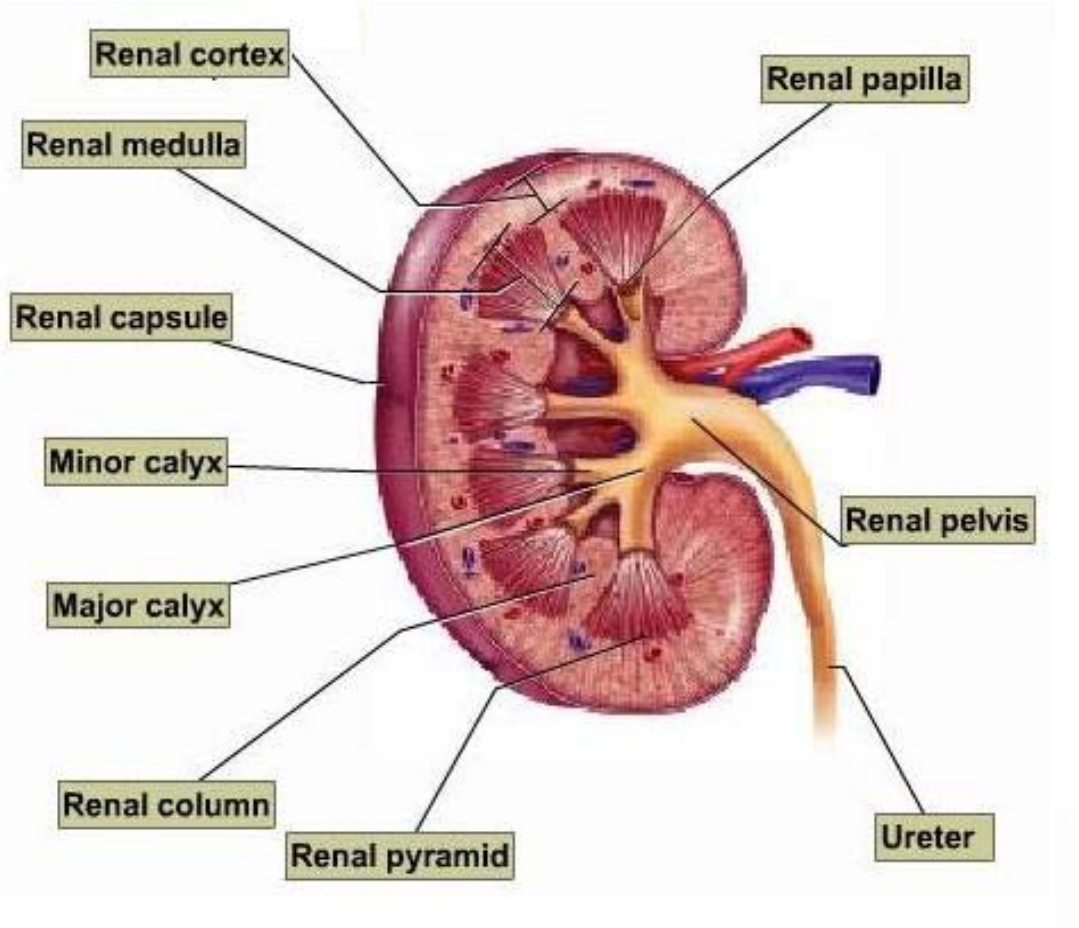


Figure 2.1 Illustration of the kidney

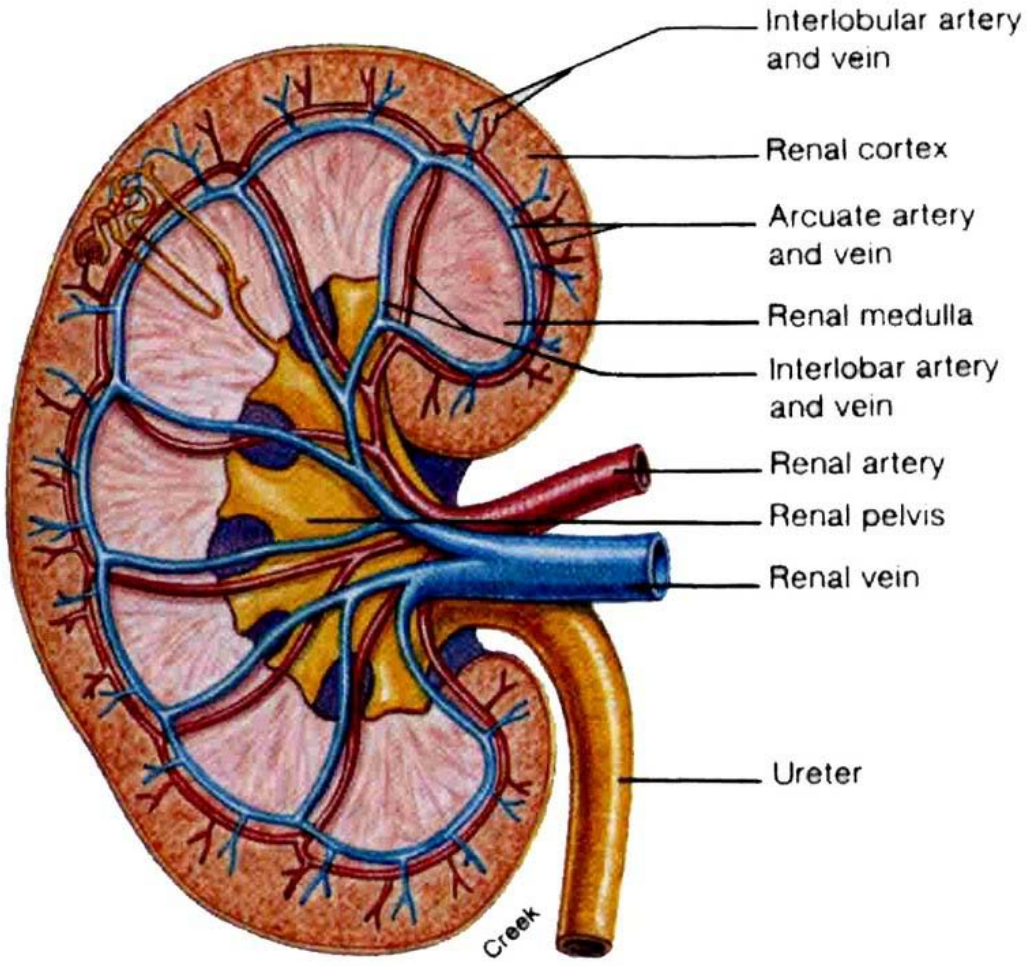
Adopted from :

http://www.comprehensivekidneyfacts.com/images/KidneyAnatomy.jpg&imgrefurl.

The kidneys receive blood from the renal arteries, branch of the abdominal aorta. It receive approximately 20% of the cardiac output. Each renal artery gives branch into segmental arteries, dividing further into interlobar arteries which penetrate the renal capsule and extend through the renal columns between the renal pyramids. The interlobular arteries then supply blood to the arcuate arteries that run through the boundary of the cortex and the medulla. Each arcuate artery supplies several interlobular arteries that feed into the afferent arterioles that supply the glomeruli (figure 2.1b).

The interstitium is functional space beneath the individual glomerulus which are rich in blood vessels. Scarring or congestion of this area will cause kidney dysfunction and failure. After filtration, the blood drains into venules network that converge into interlobular veins then into the renal vein.

The kidney is unique as it has two capillary beds arranged in series, the glomerular capillaries which are under high pressure for filtering, and peritubular capillaries which are situated around the tubule and are at low pressure (figure 1). This permits large volume of fluid to be filtered and reabsorbed. Each kidney consists of one million nephrons (P. Stewart, 1998).



Source: Fox, S.I., Human Physiology, 6th ed., pg. 529.

Figure 2.2 Renal blood supply

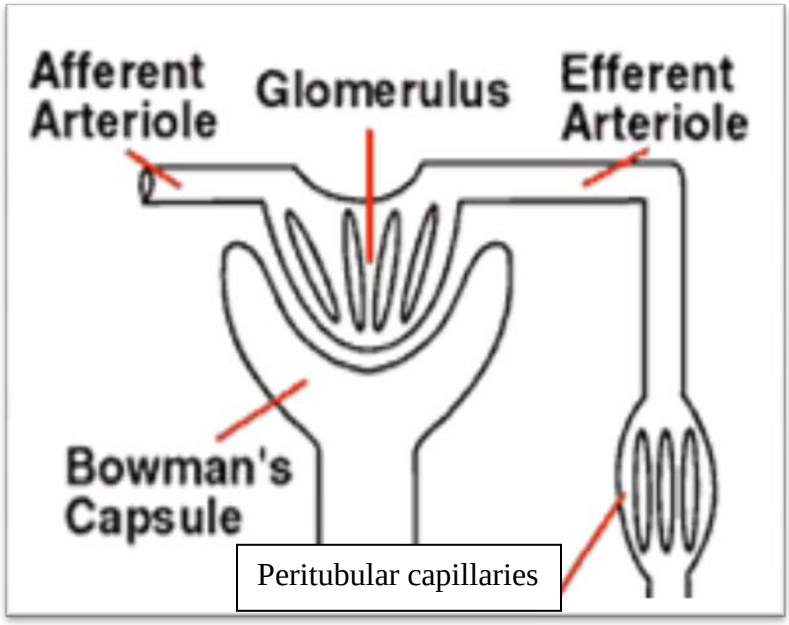


Figure 2.3 : Renal anatomy

Adopted from Physiology of the Kidney, P. Stewart, Update in Anaesthesia (1998).

Filtration takes place through the semipermeable walls of the glomerular capillaries which are almost impermeable to proteins and large molecules. The glomerular filtrate is formed by squeezing fluid through the glomerular capillary bed. The hydrostatic pressure is controlled by the afferent and efferent arterioles, and provided by arterial pressure. About 20% of renal plasma flow is filtered every minute (125 ml/min). This is known as glomerular filtration rate (GFR) (P. Stewart, 1998).

Autoregulation will keep the hydrostatic pressure fairly constant in order to keep renal blood flow and GFR relatively constant. When there is a change in arterial blood pressure, there is constriction or dilatation of the afferent and efferent arterioles. Autoregulation of GFR is achieved by autoregulation of renal blood flow and a feedback mechanism known as 'glomerular tubular balance' where if there is a decrease in GFR, the fluid flow rate within the tubule will be decrease (P. Stewart, 1998).

The function of the renal tubule is to reabsorb selectively about 99% of the glomerular filtrate. The proximal tubule reabsorbs 60% of all solute, which includes 100% of glucose and amino acids, 90% of bicarbonate and 80-90% of inorganic phosphate and water. At loop of Henle, there is greater time for reabsorption of sodium and chloride ions causing concentrated urine. The final concentration of urine occurs at distal tubule and collecting duct where it depends upon the amount of antidiuretic hormone (ADH) secreted by the posterior lobe of the pituitary. The presence of ADH

causing distal tubule and collecting duct become permeable to water therefore large quantities of dilute urine is formed (P. Stewart, 1998).

To conclude, there are so many functions of the kidney which include regulation of the water and electrolyte content of the body, retention of substances vital to the body such as protein and glucose, maintenance of acid/base balance, excretion of waste products, water soluble toxic substances and drugs as well as endocrine functions.

2.2 Measurement of renal function

Many techniques have been used to study the renal function. It is important whenever renal disease is suspected or careful dosing of nephrotoxic drugs is required. There are various methods used to measure the renal function as for follows:

2.2.3 Glomerular filtration rate (GFR)

GFR is the volume of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time (Physiology at MCG). GFR can be calculated by measuring any chemical that has steady level in the blood, and is freely filtered but neither reabsorbed nor secreted by the kidneys. The rate measured is the quantity of the substance in the urine that originated from a calculable volume of blood. GFR is typically recorded in units of volume per time.

$$\text{GFR} = \frac{\text{Urine concentration x urine flow}}{\text{Plasma concentration}}$$

2.2.2 Inulin

The ideal way to estimate the GFR is to measure the clearance of inulin that is freely filtered by glomeruli and does not undergo resorption or secretion. It has been established as a gold standard for measuring physiologic GFR. However, it is time consuming and not practical in routine clinical setting as it requires timed collection of blood and urine as well as continous inulin infusion (Delpassand *et al*, 2000).

2.2.3 Creatinine clearance

Creatinine clearance rate is the volume of blood plasma that is cleared of creatinine per unit time and is useful measure for approximating the GFR. Creatinine is produced naturally by the body (creatinine is a metabolite of creatine, which is found in muscle). It is freely filtered by glomerulus, but also actively secreted by the renal tubules in very small amount such that creatinine clearance overestimates actual GFR by 10-20% (Cockcroft, 1976). Unlike precise GFR measurements involving constant infusions of inulin, creatinine is already at a steady-state concentration in the blood and so measuring creatinine clearance is much less cumbersome.

2.2.4. Estimated creatinine clearance rate (eCcr) using Cockcroft-Gault formula

eCcr using Cockcroft-Gault Formula commonly used to estimate the creatinine clearance which in turn estimates GFR. It employs creatinine measurements and patient's weight to predict the creatinine clearance (Cockcroft, 1976). This formula expects weight to be measured in kilograms and creatinine in mg/dL. The resulting value is multiplied by a constant of 0.85 in female patient. The formula is as follows:

$$\text{eCcr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine (mg/dL)}}$$

2.2.5 Estimated GFR (eGFR) using Modification of Diet in Renal Disease (MDRD) formula.

Estimated GFR (eGFR) most commonly calculated using the ‘4-variable Modification of Diet in Renal Disease (MDRD). This formula is named after the US modification of diet in renal disease study (Levey *et al*, 1999). The variables that included in this formula are age, sex, race and serum creatinine concentration. However, the adjustment for race in MDRD equation is limited to African-American and not validated in other race and population (Levey *et al*, 1999).

For creatine in mg/dL:

eGFR = 186 x serum creatinin $\cdot^{1.154}$ x age-$^{0.203}$ x [1.21 if black] x [0.742 if female]

For creatinine in µmol/L:

eGFR = 32788 x serum creatinin $\cdot^{1.154}$ x age-$^{0.203}$ x [1.21 if black] x [0.742 if female]

2.3 Perfusion Imaging

With emerging of current technology, perfusion imaging studies can give the anatomical as well as functional information of various organs in the body, such as brain, kidney, liver as well as myocardium ((Miles *et al*, 2003, Dahini, *et al*, 2007). It is also useful in Oncology (Miles *et al*, 2003). Currently, there are many available techniques of assessing perfusion using the radiological imaging tools which include nuclear medicine study using radiopharmaceuticals, electron beam computed tomgraphy, magnetic resonance imaging as well as perfusion study using multi detector computed tomography.

The demands on perfusion study on different clinical settings are different. In context of stroke, perfusion is reduced with the aim of therapy being restoration of normal perfusion. To evaluate ischaemic tissue, perfusion values must be related to known ischemic threshold, and hence absolute quantification of blood flow volume per unit tissue is essential. In Oncology, tumour perfusion imaging exploits the increase in perfusion that results from tumour neovascularization (Miles *et al*, 2003).

2.3.1 Nuclear medicine

Procedures using radiopharmaceuticals have been proposed as rapid, less invasive, and reliable alternatives for estimating GFR. Tc-99m DTPA is primarily eliminated through glomerular filtration, and thus plasma clearance of Tc-99m DTPA can estimate the GFR (Stacy *et al,* 1966). However, accurate determination of the plasma concentration of the injected radiotracer requires analysis of Tc-99m DTPA levels in multiple blood samples obtained in several hours to avoid less accurate results by using single blood sample method (Fisher *et al,* 1975).

GFR has also been determined by measuring renal uptake of Tc-99m DTPA using a gamma camera, thus eliminating the need for multiple blood samples (Nielsen *et al*, 1997) however it tends to underestimate or overestimate the background activity and has imperfect correction of estimated renal function for renal depth (Fawdry, Ginjaume, Takaki *et al,* 1993). Delpassand *et al* (2000) reported that measuring the GFR using a dual-detector gamma camera and calculating the geometric mean of renal activity yields relatively accurate results and reduced the time required for acquisition procedures compared to single-detector cameras.

2.3.2 Electron beam computed tomography (EBCT)

Fast scanning rate available with EBCT provides high spatial and temporal resolutions required to accurately record the transit of bolus of contrast medium for calculation of perfusion (Rumberger et al, 1987) and to delineate the corticomedullary junction required for measurement of cortical and medullary volumes (Lerman *et al*, 1990).

Lerman *et al* (1990) reported that EBCT estimates of single whole kidney, cortical, and medullary perfusions and volumes are highly reproducible in normal humans, and may be useful to advance understanding of renal involvement in human disease. It is accurate and minimally invasive. Because of radiation exposure and the need for contrast media, EBCT may be of limited use in patients with greatly impaired renal function. Furthermore EBCT is not widely available in this country thus limiting its use for the perfusion study.

2.3.3 Renal perfusion measurement by MRI

Functional information also can be obtained by using magnetic resonance imaging (MRI) (Martin *et al*, 2010). Renal perfusion can be assessed by diffusion weighted MRI (Powers *et al*, 1991) or by MRI with arterial spin tagging (Roberts *et al*, 1995). However these methods are technically challenging and are characterized by a low signal to noise ratio and a reduced spatial resolution. By performing dynamic MRI during the injection, the transit of contrast medium through the kidney can be followed. Differences from the normal response profile have been observed in ischaemic kidneys (Trillaud *et al*, 1996), renal failure (Trillaud *et al*, 1995) and after renal transplantation (Low *et al* 1998). However perfusion study by MRI is more time consuming and the passage of the contrast medium in the glomerulus and the renal tubules cannot be modeled by vascular-interstitial bicompartmental system usually used in tracer kinetics (Hermoye, *et al*, 2003).

2.3.4 CT perfusion and its clinical applications

Computed tomography has ability to show not just structural information but, through CT perfusion, can provide functional information. The development of conventional computed tomography (CT) , with its cross-sectional imaging capabilities, has eliminated superimposition problems observed with some other methodologies and allowed accurate non invasive determination of whole kidney volume (Moss *et al*, 1981). CT assisted dynamic perfusion imaging or CTP has evolved in recent years with the introduction of the multi-slice spiral technique, the use of study protocols with lower injection rates and improved evaluation programmes. Eventhough CT perfusion (CTP) and MR perfusion (MRP) utilize contrast agents with similar dynamic scanning protocols, CTP has certain advantages over MRP (Hoeffner *et al*, 2004). CTP can be performed in many institutes throughout the day by using ordinary scanners with a short examination time. It is also free from ferromagnetic hazards that are caused by MRI magnets (Sasaki *et al*, 2006).

Due to requirement for rapid image acquisition and processing, CTP measurements through the 1980s were largely confined to research studies of renal or myocardial blood flow using electron beam CT systems, however the electron-beam CT scanners are not widely available (Lerman *et al*, (1996). Multidetector helical CT scanners are widely available and offering high spatial and temporal resolution (Jaschke *et al*., 1990). It may provide reliable estimates of renal hemodynamics and function. In this study, perfusion data including MIP, blood flow (BF), blood volume (BV), mean

transit time (MTT) and time to peak (TTP) at the region of interest (ROI) were calculated for each side.

CTP has been found to be useful for diagnosis of cerebral ischemia and infarction as well as evaluation of vasospasm after subarachnoid heamorrhage. It also been used for assessment of cerebrovascular reserve by using acetazolamide challenge in patients with intracranial vascular stenosis who are potential candidates for bypass surgery or neuroendovascular treatment, for the evaluation of patients undergoing temporary balloon occlusion to assess collateral flow and cerebrovascular reserve and for assessment of microvascular permeability in patients with intracranial neoplasms (Hoeffner *et al*, 2004).

In stroke, brain areas with disruption to perfusion can be detected without delay directly after the onset of the clinical symptoms. Studies show that conventional CT, together with the parameter images from PCT, enables the physician to make a distinction between the irreversibly damaged infarct core and the potentially reversibly damaged infarct penumbra (Wiesmann, 2006). In retrospective study, Eastwoods *et al* (2003) demonstrated a statistically significance difference in cerebral blood flow (CBF), cerebral blood volume (CBV) and MTT in the symptomatic hemisphere in patients presenting with acute MCA stroke. The thresholds for ischaemia that were chosen are : CBF of 0-10 ml/100g/min, CBV of 0-1.5 ml/100 g and MTT of greater than 6 seconds. They found that the extend of regional abnormalities on the perfusion maps was greatest

with MTT followed by CBF and CBV thus MTT maps may be the most sensitive indicators of stroke, and changes in CBF and CBV being more specific for distinguishing ischemia from infarction. Representative image of colour coded relative cerebral blood flow was demonstrated in figure 2.4.

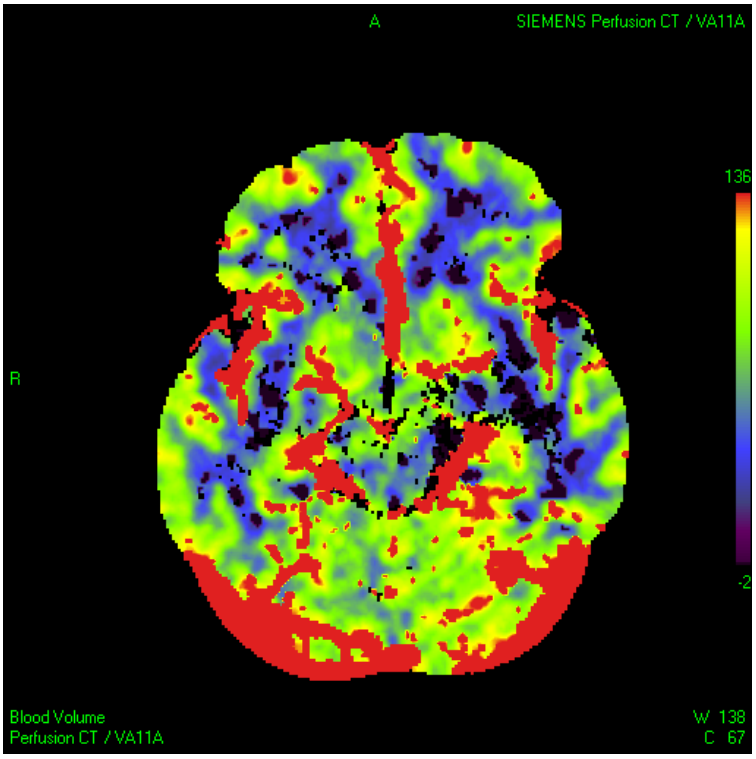


Figure 2.4 A colour coded representation of differences in relative Cerebral Blood Volume.

(Adopted from CT perfusion in neuroimaging, Zainul Ibrahim Zainuddin).

In chronic liver disease, important changes occur in the liver circulation. Van Beers *et al* (2001) found that liver perfusion, arterial fraction, and MTT but not the distribution volume were significantly altered in cirrhosis. Liver perfusion was significantly decreased where as the arterial fraction and MTT were significantly increased in patient with liver cirhhosis. The distribution volume did not differ significantly . These findings show the importance marker of liver function. CTP can be used as non invasive tool to quantify hepatic perfusion parameters in chronic liver disease.

In oncology, CTP provides information of incremental benefit in diagnosis, staging, assessment of tumour grade, prognosis and therapy monitoring (Miles and Griffiths, 2003). The basis for the use perfusion CT in oncology is that the microvascular changes in angiogenesis are reflected by increased tumour perfusion (Miles *et al*, 2000). Diagnostic application of CTP applied on distinction of benign from malignant lesions such as pulmonary nodule that were indeterminate on conventional CT, demonstrated peak enhancement of nodule has sensitivity of 98% and specificity of 58% in the diagnosis of malignancy (Swensen *et al*, 2000). There is evidence that quantification of enhancement within lymph nodes can aid in nodal staging of cancer where conventional CT relying on size criteria alone, fails to detect small tumour-bearing nodes and falsely diagnose enlarged reactive nodes as malignant (Fukuya *et al*, 1995).

CTP may also improve staging by demonstrating occult hepatic metastases which have been identified as localized areas of high perfusion (Leggett *et al*, 1997 and Dugdale *et al,* 1999). Tumour grading with CTP may also be of value when biopsy is difficult or when there is propensity for tumour grade to change with time. In lymphoma, CTP values have been shown to reflect tumour grade with perfusion above 0.5 ml/min/ml indicates high or intermediate grade tumour (Dugdale *et al,* 1999). In cerebral glioma, high grade tumours demonstrate increased blood volume and heterogeneity on blood volume images (Leggett *et al*, 2000).

The determination of tissue perfusion using CT is based on examining relationships between the arterial, tissue and venous enhancement after the introduction of a bolus of contrast material. Repeated rapid CT scans are acquired at the same location to allow the determination of time-attenuation curves (TAC). Deconvolution, slope and moments methods have been developed for analyzing these curves to obtain a perfusion value. All the techniques are based on the intravenous administration of iodine based CT contrast material and the fact that the change in attenuation due to this contrast material is directly proportional to the concentration of the contrast material. This technique makes use a peripherally administers venous bolus contrast media. Transient changes in blood vessel density can be presented by contrast media as it makes its first pass in the perfused tissue. Perfusion maps of good quantitative quality have been obtained in humans with injection rates as low as 1.5mL/sec (Nabavi DG *et al*., 1999).

Close to 100% of the intravenously injected Iohexol (contrast material) is excreted unchanged through the kidneys (mainly by glomerular filtration rate) within 24 hours in patient with normal renal function. The maximum urinary concentration of iohexol appears within approximately 1 hour after injection. The elimination half life is approximately 2 hours in patients with normal renal function. The enhancement, as expressed as a CT number or Hounsfield Unit (HU), can be directly used in tracer based techniques. The series of images obtained as the bolus of contrast material washes into and out of the tissue must contain at least one non contrast-enhanced image to act as baseline. The baseline image is subtracted either on a pixel by pixel or regional basis, from the remaining image set to obtain time enhancement data. The use of region of interest allows the generation of organ, regional or pixel time enhancement curves, also termed TACs (K A Miles, 2003). Any increase in Hounsfield units is directly proportional to the iodine concentration in the region (Yonas *et al*, 1984). Data acquisition is made at a preselected level and dynamic sequential acquisition led to the technique to be known as dynamic CT perfusion.