AUGMENTATION INDEX IN SPONTANEOUS INTRACEREBRAL HEMORRHAGE AND ITS RELATIONSHIP WITH OUTCOME

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ABSTRACT

Introduction

Intracerebral hemorrhage was the most disabling and least treatable form of stroke. The risk factors for intracerebral hemorrhage were old age, hypertension, diabetes mellitus, hypercholesterolemia, smoking and high alcohol intake which were also associated with arterial stiffness. Augmentation index was one of the surrogate marker for arterial stiffness. The aim of the study was to determine whether high augmentation index was associated with 3-month outcome and mortality in intracerebral hemorrhage.

Research methodology

Patients with spontaneous supratentorial intracerebral hemorrhage who was admitted to Hospital University Sciences Malaysia from May 2006 till May 2008 were recruited in the study. All patients were followed up for 3 month. The following data was collected for all patients in a computerized database: demographic parameters (age, sex,) , clinical parameters (modifiable risk factors for intracerebral hemorrhage, admission Glasgow Coma Scale score , height, weigh, body mass index, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, bilateral internal carotid blood flow and augmentation index), laboratory parameters (total white cells count, hemoglobin level, platelet count, random blood sugar, serum sodium, potassium, urea, creatinine, international normalized ratio, activated partial thromboplastin time, serum total cholesterol, low density lipoprotein, high density lipoprotein and triglyceride), radiological parameters (chest X-rays findings ,CT scan brain findings), in-hospital treatment (conservative or surgical treatment), type of surgical treatment (craniotomy or

external ventricular drainage), 3-month outcome (Modified Rankin Scale score) and mortality. All data was entered into Statistical Package for Social Sciences version 12. Logistic regression analysis was carried out among significant variables to identify independent predictors of 3-month poor outcome and mortality.

Result

Sixty patients with spontaneous intracerebral hemorrhage were recruited in this prospective study. Twenty-four patients (40%) had 3-month good outcome (Modified Rankin Scale 0 till 4) and thirty-six patients (60%) had poor outcome (Modified Rankin Scale 5 & 6). Twelve (33.3%) out of thirty-six poor outcome patients had high augmentation index. Thirt-eight (63%) patients survived at 3-month follow up and twenty-two (37%) patients passed away in 3-month postictus. Ten (45.5%) out of twenty-two patients that passed away had high augmentation index. Independent predictors of 3-month poor outcome were Glasgow Coma Scale score (OR, 0.7; 95%CI, 0.450 to 0.971; P= 0.035), total white cell count (OR, 1.2; 95%CI, 1.028 to 1.453; P= 0.023), hematoma volume (OR, 1.1; 95%CI, 1.024 to 1.204; P= 0.011). The significant predictors for 3-month ICH mortality were high augmentation index (OR, 8.6; 95%CI, 1.794 to 40.940; P= 0.007) and midline shift (OR, 7.5; 95%CI, 1.809 to 31.004; P= 0.005).

Conclusion

Glasgow Coma Scale score , total white cell count and hematoma volume were the most important predictors for 3-month outcome. The significant predictors for 3-month ICH mortality in this study were high augmentation index and midline shift.

ABSTRAK

Pengenalan

Pendarahan otak adalah sejenis penyakit yang boleh mengakibatkan kehilangan keupayaan dan paling susah untuk dirawati. Risiko mendapat pendarahan otak adalah usia tua, darah tinggi, kolesterol tinggi, penggunaan arak yang tinggi dan merokok. Semua faktor tersebut berkaitan dengan kekerasan salur darah. Kekerasan salur darah boleh diukur secara tidak langsung dan namanya ialah index kekerasan salur darah. Kajian tersebut adalah untuk menganalisa sama ada index kekerasan salur darah yang tinggi merupakan salah satu faktor yang mempengaruhi perkembangan pendarahan otak yang tidak memuaskan iaitu dengan ukuran skala Rankin yang diubahsuaikan 5 & 6 dan kematian dalam masa 3 bulan.

Kaedah

Pesakit-pesakit pendarahan otak yang dirawati di Hospital Universiti Sains Malaysia dari Mei 2006 sehingga Mei 2008 telah dimasukkan dalam kajian tersebut. Semua pesakit akan disusuli perkembangan lanjut mereka untuk tempoh 3 bulan. Semua data berkenaan dengan sejarah kesihatan pesakit , tahap klinikal pesakit, keputusan makmal, keputusan X-ray dada seperti nisbah kardiotorasik >0.5, keputusan gambar tomogram berkomputer , jenis rawatan di hospital, jenis pembedahan yang dilakukan dan perkembangan pesakit dalam 3 bulan dengan skor skala Rankin Scale yang diubahsuaikan telah dimasukan ke dalam pengiraan statistik versi 12 "Statistical Package for Social Sciences". Analisa "logistic regression" akan dijalankan untuk menentukan faktor-faktor yang mempengaruhi perkembangan pendarahan otak yang tidak memuaskan.

Keputusan

Kajian perspektif tersebut melibatkan enam puluh pesakit pendarahan otak. Dua puluh empat pesakit (40%) memperolehi perkembangan yang baik dan tiga puluh enam pesakit (60%) mengalami perkembangan yang tidak memuaskan. Dua belas (33.3%) daripada tiga puluh enam pesakit yang perkembangannya tidak memuaskan memperolehi index kekerasan salur darah yang tinggi. Tiga puluh lapan pesakit (63%) didapati hidup dan dua puluh duapesakit (37%) didapati meninggal dunia semasa temujanji 3 bulan. Sepuluh (45.5%) daripada dua puluh dua pesakit yang meninggal dunia mengalami index kekerasan salur darah yang tinggi. Faktor-faktor yang mempengaruhi perkembangan yang tidak memuaskan dalam 3 bulan adalah skala glasgow koma kemasukan , jumlah sel darah putih, dan volume pendarahan otak. Faktor-faktor yang mempengaruhi kematian pendarah otak dalam 3 bulan adalah index kekerasan salur darah yang tinggi dan anjalan tengah.

Kesimpulan

Faktor-faktor yang mempengaruhi perkembangan yang tidak memuaskan dalam 3 bulan adalah skala glasgow koma kemasukan , jumlah sel darah putih dan volume pendarahan otak dan faktor-faktor yang mempengaruhi kematian pendarah otak dalam 3 bulan adalah index kekerasan salur darah yang tinggi dan anjalan tengah.

List of Tables and Figures

CHAPTER 1: INTRODUCTION

Intracerebral hemorrhage (ICH) was refers to spontaneous , nontraumatic bleeding from intraparenchyme vessels (Butcher and Laidlaw, 2003). ICH , which accounts for 15-30 % of all strokes, had an estimated incidence of 37,000 cases per year. (Thompson *et al.*, 2007) . Despite the improvement in the neurointensive care, the morbidity and mortality of ICH remain high. The 6 month morbidity and mortality of ICH was 30-50% and only 20% regain functional independence at 6 months (Sacco RL, 1994). The overall hospital cost for ICH care was also very expensive (Christensen *et al.*, 2008, Russell *et al.*, 2006, Yoneda *et al.*, 2005). Although the risk factors for ICH like aging, hypertension, diabetes mellitus and hypercholesterolemia were closely associated with arterial stiffness, the predictive value of augmentation index which was one of the surrogate marker of arterial stiffness remain unknown. Ghani et al had noticed 7 spontaneous intracerebral hemorrhage patients with very high augmentation index in his 2006 dissertation (Ghani, 2006) and publication (Ghani *et al.*, 2008)

The objective of this prospective study was to determine whether high augmentation index in patients with spontaneous ICH were associated with 3-month poor outcome and mortality. The 3-month outcome of ICH patients were divided into good outcome (Modified Rankin Scale Score 0 to 4) and poor outcome (Modified Rankin Scale Score 5 and 6). Various clinical, biochemical, hematological, radiological and treatment factors were also included in the study to assess their predictive value in 3-month ICH outcome and mortality.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

Intracerebral hemorrhage (ICH) was the most disabling and least treatable form of stroke. About 50% of patients with ICH die within the first month after the hemorrhage (Vermeer *et al.*, 2002). The long term outcome of ICH was not very promising despite with recent advances in neurointensive care. Several prognostic models for ICH had been previously developed and validated (Tuhrim *et al.*, 1995, Juvela, 1995, Lisk *et al.*, 1994, Hemphill *et al.*, 2001b). Prognostication of ICH was undoubtedly important to assess treatment benefits and risks. Most of the identified risk factors for developing ICH were associated with arterial stiffness like aging, hypertension, diabetes mellitus, hypercholesterolemia, smoking and high alcohol intake . As such , the non-invasive measurement of augmentation index as a surrogate marker of arterial stiffness may provide useful predictive value in ICH patients.

2.2 EPIDEMIOLOGY OF ICH

ICH was a common hospital admission to neurology and neurosurgical department. ICH accounts for 10-30% of all stroke admissions to hospital (Sacco RL, 1994). The 6 month morbidity and mortality of ICH was 30-50% and only 20% of the patients regain functional independence at 6 months (Sacco RL, 1994). The overall incidence of ICH was 12-15 cases per 100000 people per year (Gebel and Broderick, 2000). ICH was found more common in men, in elderly people, and in Asian and African Americans (Sacco RL, 1994) .The incidence of ICH increase exponentially with increasing age, with rates doubling every 10 years after age 35 years (Broderick *et al.*, 1993b) .Epidemiology

study in South East Asia reported 22% of all stroke were hemorrhagic (Misbach, 1997). In Malaysia itself, ICH accounts for 17.2% of all stroke (Ng *et al.*, 1998).

2.3 RISK FACTORS OF ICH

The important risk factors for ICH could be divided into non-modifiable and modifiable factors. Non-modifiable factors were aging (Sturgeon *et al.*, 2007) and male sex (Ariesen *et al.*, 2003). Modifiable factors include hypertension (Zia *et al.*, 2007, Brott *et al.*, 1986, Inagawa, 2007) , diabetes mellitus (Juvela, 1996) , hypocholesterolemia (Sturgeon *et al.*, 2007, Segal *et al.*, 1999), current smoker (Thrift *et al.*, 1998) and high alcohol intake (Thrift *et al.*, 1999, Ariesen *et al.*, 2003). Based on the metaanalysis study by Ariesen et al on the risk factors for ICH in general population, the crude RR for age (every 10 year increase) was 1.97 (95% CI, 1.79 to 2.16), the crude RR for sex (male vs female) was 3.763 (95% CI, 3.28 to 4.25), the crude OR for hypertension was 3.68 (95% CI, 2.52 to 5.38), the crude RR for diabetes was 1.30 (95% CI, 1.02 to 1.67), the crude OR for high alcohol intake was 3.36 (95% CI, 2.21 to 5.12) and lastly the crude RR for current smoking was 1.31 (95% CI, 1.09 to 1.58) (Ariesen *et al.*, 2003). Hypertension was the most prevalent modifiable risk factor for spontaneous ICH, accounting for about 60-70% of all cases (Brott *et al.*, 1986, Thrift *et al.*, 1998). Study by Broderick et al reported approximately 75% of ICH patient had preexisting hypertension (Broderick *et al.*, 1993a). In Northeast Malaysia, hypertension was seen in 60.7 % of patients with ICH (Muiz *et al.*, 2003). In retrospective study, high blood pressure shown to confer a two to six fold increase in the risk of ICH (Juvela, 1996). Hypertensive patient who defaulted treatment have two fold increase in the risk of ICH compared to those who were on

regular treatment. The risk of ICH in hypertensive patient found to be related to the severity and duration of hypertension (Gebel and Broderick, 2000). Cholesterol level was still the controversial risk factor for ICH as a latest case-control study involving 242 ICH patients in Japan showed hypercholesterolemia was associated with ICH (Inagawa, 2007). Presence of apolipoprotein E2 and E4 alleles increase the risk of recurrent lobar hemorrhage in amyloid angiopathy (Woo *et al.*, 2005a, O'Donnell *et al.*, 2000). The presence of apolipoprotein E4 genotype appeared to be a risk factor for lobar ICH at the age >/= 70 years (Woo *et al.*, 2005b). It had been suggested that apolipoprotein E4 expression leads to increased vascular amyloid deposition, which may explain the increased incidence of ICH (Sullivan *et al.*, 2008) .

2.4 AETIOLOGIES OF ICH

The most common cause of primary ICH was hypertension which accounts for about 60-70% of cases (Brott *et al.*, 1986, Thrift *et al.*, 1998). Chronic hypertension causes degeneration, fragmentation and fibrinoid necrosis of small intracranial penetrating arteries which eventually could lead to spontaneous rupture (Fisher, 1971). Cerebral amyloid angiopathy was the second most common cause of primary ICH which accounts for about 15% of cases (Qureshi *et al.*, 2001). This disorder was characterized by the deposition of ß-amyloid peptide in small to medium sized intracranial blood vessels which results in vascular fragility. Cerebral amyloid angiopathy commonly causes recurrent lobar hemorrhages. The secondary causes of ICH included trauma, vascular malformation, brain tumour, hemorrhagic transformation of infarct, mycotic aneurysm, cerebral venous thrombosis, coagulopathy and vasculopathy (Manno *et al.*, 2005).

2.5 CLINICAL MANIFESTATION OF ICH

The clinical presentations of the patients depend on the site of hemorrhage ,the volume of hematoma and the presence of intraventricular extension (Manno *et al.*, 2005). The most common site of bleeding were the basal ganglia (42%), lobar (40%), cerebellum (8%), brain stem (6%) and thalamus (4%) (Bogousslavsky *et al.*, 1988). ICH with intraventricular extension could cause acute hydrocephalus and high intracranial pressure. Rapid onset of focal neurological deficit with clinical signs of high intracranial pressure (abrupt change in the level of consciousness, headache, vomiting and blurring of vision) suggest a diagnosis of ICH (Mohr *et al.*, 1978). Seizures occur in approximately 10 % of all patients with ICH and in almost 50 % of patients with lobar hemorrhage (Faught *et al.*, 1989). Rapid progession to coma with motor posturing suggests massive supratentorial hemorrhage, bleeding into the brainstem or diencephalons, or acute obstructive hydrocephalus due to intraventricular hemorrhage.

2.6 DIAGNOSIS OF ICH

The diagnostic study of choice in ICH was non contrasted computed tomography (CT). The pattern and topography of the bleeding could sometime give important clues about secondary cause of ICH , for example subarachnoid blood (suggestive of aneurysm), multiple inferior frontal and temporal hemorrhage (suggestive of trauma) or fluid level (suggestive of coagulopathy). The volume of hematoma could be estimated with ABC/2 method, where A was the greatest hemorrhage diameter by CT, B was the diameter 90 degrees to A, and C is the approximate number of CT slices with hemorrhage multiplied

by the slice thickness (Kothari *et al.*, 1996). Active contrast extravasation on CT in patients with primary ICH independently predicts mortality and hematoma growth.(Kim *et al.*, 2008). Magnetic resonance imaging (MRI) was sensitive in detecting early hematoma, vascular malformation and contrast enhancing neoplasm (Manno *et al.*, 2005). Chronic lobar microbleeds on gradient echo imaging was suggestive of underlying amyloid angiopathy. Deep basal ganglia bleed in hypertensive patients older than 45 years had low yield from cerebral angiography (Zhu *et al.*, 1997) . Some CT scan features like presence of subarachnoid hemorrhage, intraventricular hemorrhage, abnormal calcification, prominent draining vein and blood extending into perisylvian or interhemispheric fissure should proceed with angiographic study especially in non hypertensive patients (Halpin *et al.*, 1994) .

2.7 PATHOPHYSIOLOGY OF ICH

The formation of ICH was a complex and dynamic process. Early hematoma growth and perihematoma brain swelling was very common in ICH and associated with neurological deterioration and poor clinical outcome (Chang, 2007b, Brott *et al.*, 1997, Davis *et al.*, 2006). In a study of 103 patients, Brott et al found that hematomas expand in 26% of the ICH patients within one hour after the initial CT scan and about 38% of patients had an increase in hematoma volume of more than 33% within 3 hour of onset (Brott *et al.*, 1997) .The hematoma expansion has been attributed to continued bleeding from the hematoma primary source. Few factors have been associated with hematoma expansion like acute hypertension, coagulopathy, reduction of venous outflow and breakdown of blood-brain barrier (Olson, 1993, Broderick *et al.*, 1990, Kazui *et al.*, 1997, Mayer,

2003). Perihematoma brain edema could result in increased intracranial pressure and subsequently brain herniation which would cause neurological deterioration. The development of brain edema was secondary to clot retraction with extrusion of plasma protein into the brain parenchyma. Thrombin formation may cause neural toxicity and vasogenic edema by disrupting the blood-brain barrier (Xi *et al.*, 2002). The presence of ischemic penumbra in the perihematoma region have been suggested by few studies (Rosand *et al.*, 2002, Siddique *et al.*, 2002). However, some recent CT perfusion, PET and MRI studies had not shown tissue ischemia in perihematoma brain regions (Schellinger *et al.*, 2003, Zazulia *et al.*, 2001, Fainardi *et al.*, 2008). Increasing evidence suggests that inflammatory mechanisms were involved in the progression of ICH-induced brain injury. Inflammation was mediated by cellular components, such as leukocytes and microglia, and molecular components, including prostaglandins, chemokines, cytokines, extracellular proteases and reactive oxygen species (Wang and Dore, 2007). Beside this, thrombin formation, red blood cell lysis, and iron toxicity also play a major role in ICH-induced injury (Hua *et al.*, 2007).

2.8 PROGNOSIS OF ICH

Mortality of ICH approaches 50% at one year (Vermeer *et al.*, 2002). 30-day mortality rate of ICH is 35-52% and half of the deaths occur in the first 2 days (Broderick *et al.*, 2007). Numerous clinical studies had been conducted to define the predictors of outcome in ICH. The most consistent predictors were poor Glasgow Coma Score on admission (Karnik *et al.*, 2000a, Marti-Fabregas *et al.*, 2003, Roquer *et al.*, 2005b, Togha and Bakhtavar, 2004, Muiz *et al.*, 2003, Schwarz *et al.*, 2000) and hematoma volume (Hanel

et al., 2002a, Delgado *et al.*, 2006, Roquer *et al.*, 2005b, Togha and Bakhtavar, 2004, Nilsson *et al.*, 2002). Other clinical predictors were like age (Smajlovic *et al.*, 2008), hypertension (Smajlovic *et al.*, 2008), ischemic heart disease (Tetri *et al.*, 2008) , atria fibrillation (Tetri *et al.*, 2008), coagulopathy (Naval *et al.*, 2008) and antiplatelet usage (Lacut *et al.*, 2007, Naval *et al.*, 2008, Saloheimo *et al.*, 2006, Toyoda *et al.*, 2005, Roquer *et al.*, 2005b) . Study conducted by Ahmed et al involving 221 patients showed systolic blood pressure greater than or equal to 180 mm Hg (odds ratio = 2.7, P = 0.03) was a predictor of ICH mortality (Ahmed *et al.*, 2001). A total of 1701 patients with intracerebral hemorrhage analyzed by Terayama et al reported that increased mean arterial pressure was associated with increased mortality (Terayama *et al.*, 1997). Retrospective study with 87 ICH done by Dandapani et al showed marked elevated blood pressure on admission adversely affect the ICH prognosis (Dandapani *et al.*, 1995). A few studies had found some serum markers that carries poor outcome in ICH , for example hyperglycemia (Godoy *et al.*, 2008, Kimura *et al.*, 2007a, Naval *et al.*, 2008, Roquer *et al.*, 2005b, Passero *et al.*, 2003), elevated cardiac troponin I level (Sandhu *et al.*, 2008, Hays and Diringer, 2006), raised matrix metalloproteinase 3 (Alvarez-Sabin *et al.*, 2004), raised alpha tumour necrosis factor and heat shock protein 70 (Fang *et al.*, 2007). Roquer et al reported low serum cholesterol and triglyceride levels obtained in 184 patients during the first hours after ICH were strong independent predictors of in-hospital mortality in patients with spontaneous supratentorial ICH (Roquer *et al.*, 2005a). A prospective study conducted by Marti-Fabregas et al involving 48 spontaneous supratentorial ICH patients reported pulsatility Index (PI) of the unaffected hemisphere was the predictor of death in acute ICH (Marti-Fabregas *et al.*, 2003). Study on the

impact of infection on length of intensive care unit stay after ICH by Ohwaki et al revealed that complicating infection was an independent predictor of a prolonged ICU stay in patients with ICH. Few studies revealed hematoma growth is an independent determinant of both mortality and functional outcome after ICH (Chang, 2007a, Davis *et al.*, 2006, Fujii *et al.*, 1998). Associated intraventricular hemorrhage and hydrocephalus were important predictors of poor outcome in ICH (Razzaq and Hussain, 1998). Many studies had revealed associated intraventricular hemorrhage carries poor outcome in ICH (Smajlovic *et al.*, 2008, Steiner *et al.*, 2006, Bhattathiri *et al.*, 2006, Roquer *et al.*, 2005b, Togha and Bakhtavar, 2004). Early care limitations were independently associated with both short- and long-term all-cause mortality after intracerebral hemorrhage (ICH) (Zahuranec *et al.*, 2007). Hemphill et al conducted a retrospective study to investigate the outcome predictors of ICH concluded Glasgow Coma Scale score ($P<0.001$), age >/=80 years ($P=0.001$), infratentorial origin of ICH ($P=0.03$), ICH volume ($P=0.047$), and presence of intraventricular hemorrhage ($P=0.052$) were factors independently associated with 30-day mortality (Hemphill *et al.*, 2001a).

2.9 HISTORY OF ARTERIAL PULSE WAVEFORM

The shape of the arterial pressure pulse contain hemodynamic information which could be used to supplement the conventional measurement of blood pressure. The interaction between the heart as a pump and the arterial system as the load with similar values of systolic and diastolic pressures could be associated with many different pulse wave shapes (Nichols, 1998). The elastic and geometric properties of the arteries caused the arterial pressure pulse to change its shape as it travels along the arterial tree (Mills *et al.*,

1970). Fredrick Akbar Mahomed, at Guys Hospital in London, was the first one described the changes in the shape of the arterial pulse with age and hypertension in 1872 (Mahomed, 1872). In the early days the arterial pulse wave was recorded by a sphygmograph as shown in figure 2.9 , a device strapped to the wrist with a set of levers moving in response to the pulse and writing on a moving paper strip.

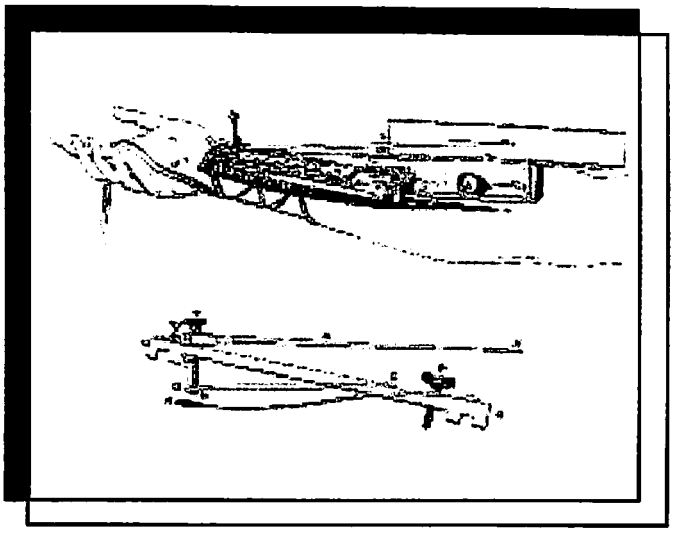


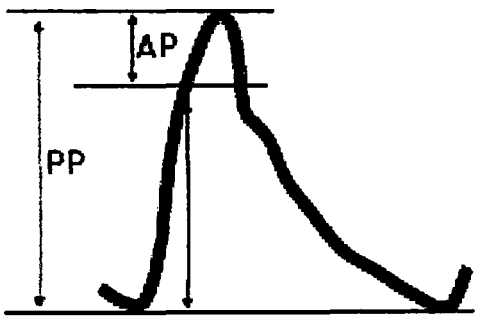
Figure 2.9 : Illustration of the Sphygmograph developed by French physiologist Etienne-Jules Marey (as described by B. Sanderson in 1867 in "The handbook of the sphygmograph", Hardwiche, London). The lower part showed the lever mechanism in profile.

The study of blood flow in arteries by McDonald (Nichols, 1998) was the fundamental of the development of SphygmoCor which was an integrated system of pulse wave analysis. SphygmoCor derived the central aortic pressure waveform non-invasively from the pressure pulse recorded at a peripheral site (example radial artery). This system provided accurate recording of the peripheral pulse by means of applanation tonometry and using a validated generalized transfer function of the upper limb across the adult population to

generate central aortic pressure waveform. The augmentation index (AIx) was then calculated from the derived central aortic pressure waveform.

2.10 DEFINITION OF AUGMENTATION INDEX (AIx)

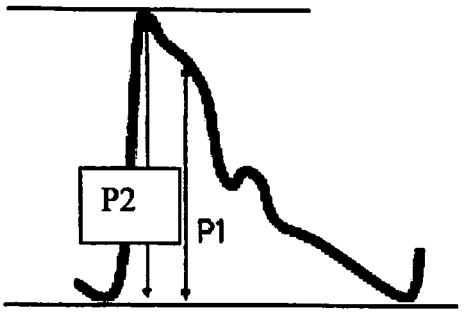
The central AIx had been defined as the ratio of central augmented pressure to the central pulse pressure as shown in figure 2.10 (Kelly *et al.*, 1989). The arterial pulse waveform consists of a forward pressure wave generated by left ventricular ejection and a reflected wave produced by the peripheral arterial tress. The forward and reflected waves will merge at one point and produced an augmented wave. As the stiffness of arterial system increases, the transmission velocity of both forward and reflected waves increase which will cause the reflected wave to arrive earlier in the central aorta and augments pressure in late systole. The central (aortic) and peripheral (radial) pressure waveform were slightly different as shown in figure 2.10a and 2.10b .



AIx |%| = AP / PP

Figure 2.10a : Central aortic pressure waveform characteristics

(AIx, augmentation index ; AP, augmented pressure; PP, pulse pressure)



AIx (%) = P1 / P2

Figure 2.10b: Radial artery pulse pressure waveform characteristics

(AIx, augmentation index; P1, the amplitude of late systolic peak; P2, the amplitude of early systolic peak)

2.11 MEASUREMENT OF THE AUGMENTATION INDEX

The direct aortic pulse wave measurement was invasive and cannot be performed routinely. Thus , the non-invasive method like applanation tonometry had been used to measure the peripheral pulse waveform and then convert it into aortic waveform by using the computer software and complex transfer function. The tonometry consist of a small transducer with sensitive high fidelity pressure tip which can detect the dynamic changes in force or volume in the artery due to the expansion of the segment of artery underlying the transducer. The principle of applanation tonometry, which was used to measure intra-ocular pressure for the assessment of glaucoma and its response to treatment , had been applied to develop a a pencil-type hand-held probe with the sensing element at the tip to obtain a high-fidelity artery pulse wave signal without penetrating the skin or blood vessels. The applanation tonometry could be applied on either the carotid or radial artery to derived the central AIx. The radial artery pulse wave needed a generalized transfer function to derive the central AIx. The application of the applanation tonometry on the

carotid artery needs technical expertise and can be very uncomfortable to the patient. This technique was not suitable for subjects with carotid atherosclerotic disease. The radial artery was easier to access and the application of tranducer was also more comfortable for the patient. The transfer function was a mathematical model which can reconstruct aortic pulse waveform from the non-invasive radial artery pulse waveform. The transfer function was determined by the physical properties of the arterial system, such as arterial diameter, wall elasticity, wall thickness, amount of branching, and the condition of the peripheral vascular beds. It was expected that there would be some difference in the overall transfer function among individual subjects due to different brachial vasculature. However, it was found that the main components of the transfer function do not change markedly between normal adults with aging. Studies of pulse wave velocity (a parameter which was related to arterial stiffness) had shown that most of the ageing changes occur in the aortic trunk and not in the arteries of the arm (Avolio *et al.*, 1983, Avolio *et al.*, 1985). This indicates that functional elastic properties of the arteries in the arm were reasonably constant with age. Few studies had validated the generalized transfer function to generate the central aortic pressure waveform. Kanamanoglou et al had shown good consistency between the measured and derived waveforms by using the generalized transfer function (Karamanoglu *et al.*, 1993). The study by Chen et al had validated the use of the generalized transfer function under normal conditions and during haemodynamic transients (like Valsalva manoeuvre, abdominal compression, nitroglycerin, or vena caval obstruction) (Chen *et al.*, 1997). Pauca et al had confirmed the use of a generalized transfer function to synthesize radial artery pressure waveforms which can provide substantially equivalent values of aortic systolic, pulse, mean, and