The Relationship Between Digital Vascular Function and Combination Hypertension Therapy in Patients with Newly Diagnosed Hypertension

Chun-Chung Lin[1], Hsien-Jung Lo[1], Chung-Ming Tu[1], Wei-Quan Fang[2], and Ai-Hsien Li[1]

[1]Division of Cardiology, Far-Eastern Memorial Hospital, New Taipei City, Taiwan
[2]Taiwan Clinical Trial Statistical Center, Training Center and Pharmacogenomics Laboratory, Taipei City, Taiwan

Abstract

Endothelial dysfunction plays a key role in cardiovascular diseases and hypertension is associated to endothelial dysfunction. Measuring digital vascular function through peripheral arterial tonometry is an innovative method to evaluate endothelial function. The aim of this study was to evaluate the changes in digital vascular function in hypertensive patients before and after anti-hypertension therapy. We recruited 54 newly diagnosed hypertensive patients and 40 normotensive participants. Among these 54 hypertensive patients, 29 received a complete 3 months combination anti-hypertension therapy with angiotensin-converting enzyme inhibitors (or angiotensin receptor antagonist) and calcium channel blockers. Their digital vascular function were evaluated through peripheral arterial tonometry before and after anti-hypertensive therapy and compared with the normotensive participants' data. The percentage of endothelial dysfunction was nonsignificantly higher (13% V.S 7.9%, *P* .34) in hypertensive group than in normotensive group. After combination anti-hypertensive therapy, the reactive hyperemia indices (RHIs) of the majority of the patients (65%) improved albeit nonsignificantly (mean RHI before therapy 2.07 +/- 0.39, mean RHI after therapy 2.03 +/- 0.79, *P*= .825). However, the hyperemia ratio of 0.879 of the control arm was a significant predictor (*P* .0273 and 0.003 respectively) of the RHI response of after pharmacological therapy. The hypertensive patients showed a non-significant higher percentage of the endothelial dysfunction than did the normotensive participants. Combination therapy did not significantly improve RHI. A hyperemia ratio of 0.879 of the control arm was a significant predictor of the response of RHI after pharmacological therapy. (J Intern Med Taiwan 2015; 26: 268-276)

Key Words: Endothelial function, Reactive hyperemia index, Hypertension, Combination therapy

Introduction

Endothelial dysfunction plays an important role in the pathogenesis of atherosclerosis and several cardiovascular diseases. Various techniques, such as flow-mediated dilatation, plethysmography, pulse wave analysis and pulse contour analysis, have been developed for assessing vasomotor function.[1] Peripheral arterial tonometry (PAT) (EndoPAT 2000; Itamar medical, Caesarel, Israel, Fig 1a) is one of the techniques that non-invasively evaluates the endothelial function by assessing the pulse wave

Reprint requests and correspondence：Dr. Ai-Hsien Li
Address：Division of Cardiology, Far-Eastern Memorial Hospital, New Taipei City, Taiwan, No. 21, Sec. 2, Nanya S. Rd., Banciao District, New Teipei City, 220, Taiwan

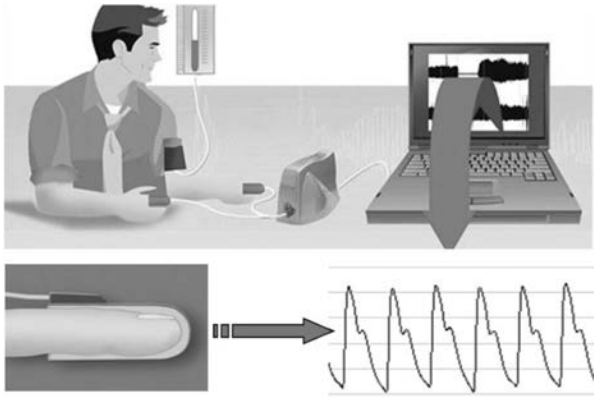
amplitude (PWA) of the fingertips. The flow-mediated vasodilatation (FMD) method measures the change in the blood flow of the unilateral brachial artery before and 5-min after compression of the forearm brachial artery, whereas the reactive hyperemia index (RHI) is calculated as the ratio of the pulse amplitude of bilateral digits before and 5-min after compression of the unilateral brachial artery (fig 1). RHI is considered more representative of the microvascular function because of by the measurements taken from the small resistant vessels of the digits.

Essential hypertension is strongly associated with vascular atherosclerosis and is a major risk factor for advanced cardiovascular diseases. A study using FMD and intraarterial injections of acetylcholine reported endothelial dysfunction in essential hypertension.[2] Furthermore, endothelial function can be improved through anti-hypertensive therapy, specifically by using angiotensin-converting enzyme inhibitors (ACEI) and calcium-channel blockers (CCB).[3,4] However, PAT has rarely been used for evaluating the longitudinal association between the digital vascular function and essential hypertension. Therefore, we used PAT and conducted this prospective study for assessing the changes in the digital vascular function in hypertensive patients before and after ACEI (or angiotensin-receptor blocker (ARB)) and CCB combination anti-hypertension therapy (A+C combination therapy).

Methods

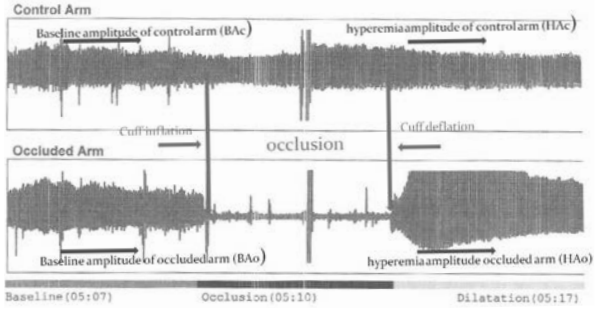
Study Population

Hypertensive patients were enrolled from the outpatient department of Far Eastern Memorial Hospital from October 2012 to July 2013. The inclusion criteria for the hypertension group were systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg in at least 2 separate blood pressure measurements. The exclusion criteria were having diabetes mellitus, coronary artery disease, myocardial infarction, stroke or chronic kidney disease. In total, 54 newly diagnosed and



(A) measuring the RHI

RHI =(HAo/BAo)/(HAc/BAc)*baseline correction



(B)formula of RHI

Figure 1. Determination of reactive hyperemia index and digital vascular function.
RHI, reactive hyperemia index,
PAT, peripheral arterial tonometry
HAo, hyperemia amplitude of occluded arm, mean PAT amplitude between 90 secs-150 secs post occlusion of occluded arm
BAo, baseline amplitude of occluded arm, mean PAT amplitude from the baseline period of the occluded arm
HAc, hyperemia amplitude of control arm, mean PAT amplitude between 90secs- 150 secs post occlusion of control arm
BAc, baseline amplitude of control arm, mean PAT amplitude from the baseline period of the occluded arm
Baseline correction: (0.2276*ln(mean occluded baseline amplitude)-0.2)

treatment-naïve patients (mean age, 47.7 +/- 9.2 y) were enrolled in this study.

In addition, 40 normotensive participants (mean age 44.2 +/- 7.4 y) were recruited from the community as the control group for comparing the differences in the baseline digital vascular function between the 2 groups. The normotensive participants had cardiovascular risk factors similar to those of the hypertensive patients namely obesity, smoking or dyslipidemia but without any systemic diseases.

Reactive Hyperemia Index Measurements

PAT was performed using the EndoPAT 2000 (Itarmar Medical Ltd., Caesrea, Israel; Figure 1a), which consists of bilateral probes for index fingers, a pressure cuff, and a computer. The probes were placed on bilateral index fingers and beat-to-beat plethysmographic data were recorded. A baseline measurement was recorded for 5min after acclimatization for 10 min. Subsequently the test arm was compressed for 5 min by inflating the pressure cuff to 180-200mmHg or 50mmHg higher than the systolic blood pressure of the brachial artery for generating a transient ischemia of the index finger of the test arm. Then cuff deflation, a caused hyperemia in the test index finger and PWA of bilateral index fingers was recorded for additional 5 min. The hyperemia index was calculated as the ratio of average PWA recorded during 1 min (since 90-150 sec after cuff deflation) to the 3.5 min baseline PWA (figure 1b)

Protocol

Baseline measurements of the clinical cardiovascular risk factors, such as body weight and smoking history, of all participants were collected from their medical charts. Blood and urine tests were performed as a routine hypertension work – up for evaluating the levels of fasting sugar, creatinine, and urinary microalbumin. The brachial-ankle pulse wave velocity (baPWV) was measured as a vascular stiffness marker. The digital vascular function was evaluated by using the EndoPAT-2000. Furthermore, RHI, baseline pulse amplitude, hyperemia amplitude, and hyperemia ratio of bilateral arms were analyzed. All of the participants were requested to refrain from coffee and alcohol intake at least one night prior to the tests, but regular meals were allowed. Female participants in the menstruation period were evaluated after the period was completed. The baseline digital vascular function in the hypertensive patients was measured before initiating medical treatment. After completing clinical evaluations, the hypertensive patients were prescribed a fixed dose combination of ACEI and CCB (Amtrel, benzapril 10 mg + amlodipine 5 mg, Tsh Biopharm, Taiwan). If the patients were unable to tolerate A+C combination therapy because of such side effects as dry cough, another fixed dose of combination of ARB-CCB (Exforge, valsartan 80 mg + amlodipine 5 mg, Novartis) was prescribed. The medication doses were adjusted to achieve the blood pressure goal (the systolic and diastolic blood pressures < 140 mmHg, 90 mmHg, respectively). After at least 3 mo of fixed dose combination therapy either ACEI-CCB or ARB-CCB, the hypertensive patients again underwent baPWV and digital vascular function tests. During the study period, other anti-hypertensive medications were not allowed; however statins were prescribed at the discretion of the physician.

All participants provided written informed consent and this study was approved by the Institutional Review Board of Far-Eastern Memorial Hospital.

Statistical Analyses

All analyses were performed using SAS software Version 9.3 (SAS Institute Inc., Cary, NC, USA). The Student' *t*-test was used for comparing continuous variables, and the chi-square or Fisher' exact tests were used for categorical variables. Uni-

variate regression analysis was used for exploring the association between RHI and other factors. *P* value less than.05 was considered statistically significant. All data are represented as means +/- (standard deviation) (+/- SD) unless otherwise indicated.

Result

The baseline demographic characteristics and vascular parameters of the 2 groups (hypertensive and normotensive) are summarized in Tables 1 and 2. In total, 54 hypertensive patients (average age, 47.7 +/- 9.2 y) were enrolled, however, for 2 patients, the noise to signal ratio for the raw PAT data was high, these patients were excluded from the analysis. Therefore, the baseline digital vascular functions of the remaining 52 hypertensive patients were analyzed. 40 normotensive participants were enrolled and raw PAT data were lost in 2 participants. Therefore, the data of the remaining 38 normotensive participants were analyzed.

Among the hypertensive patients, 29 (55.7%) tolerated our target ACEI-CCB or ARB-CCB combination therapy well and received at least 3 months of this therapy. Among these 29 subjects, 23 (79%) received Amtrel with an average dose of 1.17 tablets per day, and 6 (21%) received Exforge with average dose of 1 tablet per day. The baseline characteristics of the normotensive and hypertensive groups are presented in Table 1. Compared with the normotensive participants, the hypertensive patients had significantly high systolic and diastolic blood pressure, heart rate, blood sugar, and blood triglycerides levels but low high-density lipoprotein (HDL) level.

The baseline parameters of the digital vascu-

Table 1. Baseline characteristics of the normotensive and hypertensive groups

Variable	Total (N=93)	Normal (N=39)	Hypertension (N=54)	P-value
Age, years	46.30 (8.71)	44.32 (7.50)	47.70 (9.29)	0.0660
Female	44 (49%)	21 (55%)	23 (44%)	0.3011
Smoking	19 (21%)	2 (5%)	17 (33%)	0.0016
SBP, mmHg	145.79 (29.21)	117.34 (13.67)	165.81 (18.58)	<0.0001
DBP, mmHg	88.58 (16.34)	74.66 (10.56)	98.37 (12.00)	<0.0001
HR, bpm	75.88 (13.94)	68.39 (10.01)	81.45 (13.91)	<0.0001
Body weight, kg	72.41 (19.56)	70.23 (24.64)	73.94 (15.08)	0.4136
Body height, cm	165.27 (8.22)	165.79 (8.83)	164.91 (7.83)	0.6151
BMI	26.43 (6.58)	25.48 (8.63)	27.10 (4.61)	0.2973
Cr, mg/dl	0.83 (0.17)	0.82 (0.17)	0.84 (0.16)	0.5979
Sugar, mg/dl	96.74 (11.26)	93.34 (7.88)	99.13 (12.66)	0.0083
CHO-T,mg/dl	198.82 (38.58)	196.29 (40.03)	200.64 (37.79)	0.5984
TG, mg/dl	128.48 (81.24)	104.32 (60.32)	145.81 (90.01)	0.0100
HDL-C, mg/dl	53.13 (14.51)	57.79 (14.60)	49.73 (13.59)	0.0085
LDL-C, mg/dl	127.04 (34.78)	123.32 (33.02)	130.04 (36.21)	0.3785
MAU, mg/dl	5.68 (15.06)	0.81 (0.46)	8.12 (18.07)	0.0595

Continuous parameters are summarized as means (standard deviations)
SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate per min; BMI, body mass index; Cr, creatinine; CHO-T, blood total cholesterol; TG, triglyceride; HDL-C, blood high density lipoprotein; LDL-L, blood low density lipoprotein; MAU, microalbuminuria.

lar function and vascular stiffness for both groups are presented in Table 2. A higher percentage (13%, 7/54) of abnormal RHI (< 1.67, quote reference) and a lower mean RHI (2.21 +/- 0.55) were observed in the hypertensive patients compared with the normotensive participants (7.9%, 3/38, mean RHI, 2.26 +/- 0.54, respectively). However, the difference was nonsignificant (p = .34 Fisher' exact test). On the other hand, baPWV was significantly high in the hypertensive group (p < 0.001). The differences in the parameters of digital vascular function including the baseline and hyperemia amplitudes between the 2 groups were nonsignificant. However, for all study participants, in contrast to the hyperemic response (mean hyperemia ratio 1.75, mean hyperemia amplitude 963) in the occluded arm after cuff deflation, a relative vasoconstrictive response (mean hyperemia ratio 0.90, mean hyperemia amplitude 549) was recorded in the control arm after cuff deflation (Table 3). Both the hyperemia ratio and hyperemia amplitude were significantly high for test arm (p < .0001).

The univariate regression analysis of the baseline cardiovascular risk factors for all participants is presented in Table 4. The results showed that RHI was positively correlated with an increased HDL level, and inversely correlated with an increased level of blood creatinine. Most cardiovascular risk factors, such as blood pressure, body weight, blood sugar and smoking, were nonsignificantly correlated with RHI.

RHI Changes after Combination Therapy

The changes in the parameters of vascular stiffness and digital vascular function after the 3 months combination therapy in 29 hypertensive patients are presented in Table 5 and Figure 2. RHI increased in 19/29 (65%) and decreased in 10/29 (34.5%) hypertensive patients; however the difference in the mean RHI was nonsignificant (mean RHI, 2.07 v.s 2.03; p .825). Moreover, the differences between the 2 groups for the parameters of digital vascular function, including the baseline and hyperemia amplitudes were nonsignificant except for baPWV, which

Table 2. Parameters of vascular physiology in the normotensive and hypertensive groups

variable	Total	Normotensive (n=38)	Hypertension (n=54)	P-value
baPWV,cm/sec	1474.18 (323.79)	1209.16 (145.49)	1660.69 (281.84)	<0.0001
RHI	2.23 (0.54)	2.26 (0.54)	2.21 (0.55)	0.6659
BAo	659.46 (423.76)	605.81 (432.88)	697.64 (417.15)	0.3164
HAo	963.11 (448.79)	882.53 (479.91)	1020.44 (420.59)	0.1542
BAc	608.76 (426.86)	548.71 (416.89)	651.49 (432.70)	0.2653
HAc	549.47 (421.40)	478.50 (405.43)	599.97 (429.09)	0.1817

Continuous parameters are summarized as mean (standard deviation)
baPWV, brachial-ankle pulse wave velocity; RHI, reactive hyperemia index; BAo, baseline amplitude of occluded arm; HAo, hyperemia amplitude of occluded arm; BAc, baseline amplitude of control arm; HAC, hyperemia amplitude of control arm

Table 3. Different vascular changes between the occluded arm and control arm

Variable	Occluded arm	Control arm	P-value
Hyperemia ratio	1.75 (0.69)	0.90 (0.23)	<0.0001
Hyperemia amplitude	963.11 (448.79)	549.47 (421.40)	<0.0001

Continuous parameters are summarized as mean (standard deviation)
Footnote: Hyperemia ratio means HAo/BAo in occluded arm, HAc/BAc in control arm. HAo, hyperemia amplitude of occluded arm; BAo, baseline amplitude of occluded arm; HAc, hyperemia amplitude of control arm; BAc, baseline amplitude of control arm

Table 4. Univariate regression analysis of reactive hyperemia index

Variable	Beta	SE	R^2	P-value
Age,years	-0.009	0.007	0.0194	0.1849
Body weight,kg	0.001	0.003	0.0024	0.6425
Body height,cm	-0.006	0.007	0.0087	0.3775
BMI	0.007	0.009	0.0069	0.4325
CHO-T,mg/dl	0.001	0.002	0.0026	0.6319
TG,mg/dl	0.000	0.001	0.0027	0.6260
HDL-C,mg/dl	0.008	0.004	0.0496	0.0348
LDL-C,mg/dl	-0.001	0.002	0.0016	0.7137
Sugar,md/dl	0.001	0.005	0.0005	0.8246
Cr,mg/dl	-0.702	0.339	0.0454	0.0413
baPWV,cm/sec	0.000	0.000	0.0029	0.6097
SBP,mmHg	-0.001	0.002	0.0043	0.5328
DBP,mmHg	0.001	0.004	0.0007	0.7968
HR,bpm	0.003	0.004	0.0068	0.4420
MAU,mg/dl	-0.008	0.006	0.0461	0.2085
Female	0.175	0.114	0.0259	0.1295
Smoking	0.160	0.142	0.0142	0.2633

BMI, body mass index, CHO-T, blood total cholesterol; TG, triglyceride; HDL-C, blood high density lipoprotein; LDL-C, blood low density lipoprotein; Cr, creatinine; BaPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate per minute; MAU, microalbuminuria.

Table 5. Changes of vascular parameters after combination therapy in 29 cases with hypertension

Variable	Hypertension (pre-treatment)	Hypertension (post-treatment)	P-value
SBP,mmHG	166.38 (17.53)	131.38 (10.85)	<0.0001
DBP,mmHg	99.41 (10.22)	81.14 (7.75)	<0.0001
HR,bpm	82.43 (14.24)	81.00 (15.10)	0.7171
baPWV,cm/sec	1676.17 (271.93)	1472.66 (213.77)	0.0025
RHI	2.07 (0.39)	2.03 (0.79)	0.8251
BAo	761.16 (487.84)	831.26 (371.09)	0.5405
HAo	1064.97 (477.19)	1095.72 (432.23)	0.7980
BAc	746.83 (499.01)	837.11 (400.74)	0.4507
HAc	700.32 (488.40)	765.94 (430.60)	0.5895

Continuous parameters are summarized as mean (standard deviation).

Footnote: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; baPWV, brachial-ankle pulse wave velocity; RHI, reactive hyperemia index; BAo, baseline amplitude of occluded arm; HAo, hyperemia amplitude of occluded arm; BAc, baseline amplitude of control arm; HAc, hyperemia amplitude of control arm.

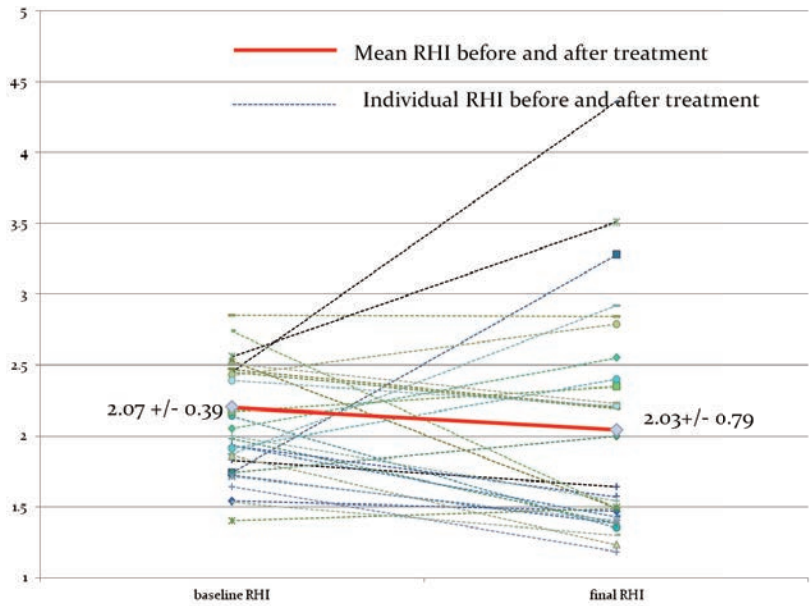


Figure 2. Spaghetti plot of changes in reactive hyperemia index by patient (29 cases undergoing combination therapy).

Table 6. Baseline hyperemia ratio of control arm (0.879) could predict the response of reactive hyperemia index to hypertension therapy in 29 cases undergoing complete combination therapy

Variable	n	RHI (before treatment)	n	RHI (after treatment)	P-value
Baseline HRc < 0.879	11	2.13 (0.38)	11	2.69 (0.82)	0.0273
Baseline HRc > 0.879	18	2.03 (0.40)	18	1.63 (0.43)	0.0003

RHI, reactive hyperemia index; HRc, hyperemia ratio of control arm.

significantly decreased after anti-hypertensive therapy (p=.0025).

Table 6 shows that one factor that significantly predicted the RHI response after anti-hypertensive therapy was the pre-treatment hyperemia ratio of the control arm (0.879; median of the hyperemia ratio of the control arm in the hypertensive patients). If the pre-treatment control arm hyperemia ratio was higher than 0.879 then the RHI was significantly decreased after anti-hypertensive therapy (p=.0003). However, if the baseline hyperemia ratio of the control arm was less than 0.879 then the RHI was significantly increased after anti-hypertensive therapy (p=.027).

Discussion

In this study, the percentage of the participants with RHI below the normal reference level was low (7.9%, 3/38) in the normotensive group and high (13%, 7/54) in the hypertensive group but with no significant differences. In addition, the mean RHI for the hypertensive group was 2.21, which was still above the quote reference (1.67). This is consistent with the findings of 2 other studies reporting mean RHI before hypertensive treatment within the normal range.[5,6]

Although hypertension is associated with endothelial dysfunction, our study did not demonstrate a significant difference in RHI between our study groups.[7] Similarly, Framingham study reported that hypertension and systolic blood pressure were marginally associated with a low hyperemic response.[8] Several possible reasons can explain our findings. First, as an innovative method for assess of the endo-

thelial function and primarily designed to replace the highly technical FMD method, the PAT system only measured the part associated with the endothelial-dependent vasodilatation of the occluded arm. Compared with the conventional methods, PAT has been shown to be moderately sensitive .[9,10] Second, the nonsignificant differences in the endothelial function between 2 groups may be caused by the relatively small sample size and relative early stage of cardiovascular disease. Third, we suspect that vessels of different sizes maybe not homogeneously involved during the process of endothelial dysfunction, resulting in disparities between the results obtained through endoPAT and FMD methods.[11,12,13]

Compared with the hyperemic changes in the occluded arm after brachial cuff deflation, a relative vasoconstriction was recorded in the control arm after cuff deflation. Another novel finding of this study was that the hyperemia ratio of < 0.879 of the control arm could predict the RHI response after pharmacological therapy. These 2 novel findings imply an intact endothelial function including both vessel dilatation and vessel constriction. Additional studies are required for determining the exact physiological importance and the underlying mechanism.

Conclusion

The newly diagnosed and treatment-naïve hypertensive patients had a relatively high percentage of low RHI than that observed in the normotensive participants; however, the difference was nonsignificant. Although the majority of the patients who received combination therapy showed improved RHI, the difference between the 2 group was nonsignificant. However, the hyperemia ratio of the control arm of 0.879 was a significant predictor of the RHI response after pharmacological treatment.

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初診斷之高血壓患者指尖血管功能與複合式藥物治療之關係

林俊忠[1] 羅顯榮[1] 杜宗明[1] 方偉泉[2] 李愛先[1]

新北市板橋區亞東紀念醫院 [1]心臟血管中心
[2]台北市台灣臨床生物統計中心

摘 要

血管內皮功能不良與許多的心血管疾病形成有關，而高血壓是許多心血管疾病與血管硬化的早期表現。過去已有文獻用FMD的方式證明高血壓的患者有血管功能異常，用周邊動脈測量儀來測量反應性充血指標(RHI)是一種新的血管內皮評估工具。吾人設計一前瞻性研究，以enoPAT機器，測量初診斷的54位高血壓患者之血管功能並與40位正常血壓族群來比較與評估高血壓患者是否有內皮功能不良，以及患者在接受目前第一線之A+C合併治療之後之血管功能參數變化。結果顯示雖然高血壓患者有較高的比例內皮功能不良但未達到統計學的意義。另外在經過三個月治療之後，雖然大部分患者RHI有改善但也未達統計學的意義。不過吾人發現“對側手”充血指數0。879是一個有統計意義的數字，可以預測病人治療後RHI改變的趨勢。同時發現相較於受側手在充血期有充血反應，對側手則出現周邊血管收縮血流減少現象。其機制與重要性不明。