Correlation between High Sensitive C-Reactive Protein and Aortic Stiffness Using Magnetic Resonance Imaging in Patients with Known/Suspected Coronary Artery Disease

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Background: *High sensitive C-reactive protein (hs-CRP), a representative of an inflammatory cascade, has been established as a crucial independent risk factor of atherosclerosis from prior studies. Like Aortic stiffness, an indirect index of arterial distensibility, has a promising role in the forecast of cardiovascular mortality and morbidity. Pulse wave velocity (PWV) via cardiac magnetic resonance imaging (MRI), is one of the most reliable parameters of aortic stiffness. Nevertheless, the relationship between these two predictors has not been explored. The present study aims to prove the hypothesis that aortic stiffness, assessed by PWV, is related to an inflammatory process.*

Objective: *To determine the relationship between hs-CRP and PWV using velocity-encoded CMR.*

Material and Method: *Ninety patients referring for CMR owing to known or suspected coronary artery disease at Siriraj Hospital were consecutively enrolled into the present study from October 2010 to February 2011. Informed consent and baseline characteristic were recorded. Aortic stiffness, as assessed by PWV using CMR, was calculated as the ratio of distance from mid ascending to descending aorta (m) divided by time delay measured at 2 according sites (sec) hs-CRP was analyzed using Immunonephelometry assay by Seimens. The correlation between PWV and hs-CRP was analyzed using Pearson correlation method.*

Results: *The authors enrolled 90 patients with 48 male (53.3%), with a mean age of 68 $\pm$ 10 years. The baseline characteristic revealed mean body mass index (BMI) 26.2 $\pm$ 4.2 kg./sq m and left ventricular ejection fraction (LVEF) 58.46 $\pm$ 20.3%. Mean hs-CRP was 7.62 $\pm$ 28.59 mg/l and PWV was 11.43 $\pm$ 5.13 m/sec. There was significant correlation between PWV and hs-CRP ($r = 0.251$, $p = 0.017$) and PWV and age (r 0.244, $p = 0.02$).*

Conclusion: *The correlation of an inflammatory marker, hs-CRP and abnormal aortic property, PWV, has been established in this study, using a concept of MRI. This potentially reflects an inflammation as a contributor to an abnormal aortic wall property.*

Keywords: *Pulse wave velocity (PWV), hs-CRP, Aortic stiffness, magnetic resonance imaging*

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Therefore, the objective of the present study is to determine whether there is correlation between CRP and arterial stiffness, measured as PWV using MRI in patients with known/suspected coronary artery diseases.

Material and Method

This is a prospective, cross sectional, single institution study undertaken with approval from the ethic committee for individual informed consent before study initiation.

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Patient population

As consecutive patients, who were suspected coronary artery disease, attended as outpatient at cardiac MRI unit, division of cardiology, Siriraj Hospital during October 2010 to February 2011. Exclusion criteria included age younger than 18 years, uncontrolled essential hypertension (BP >200/100 mmHg), severe renal impairment (creatinine clearance < 30 ml./min.), unstable coronary disease within 6 weeks, inflammatory diseases (such as sepsis, arthritis, malignancy,

connective tissue diseases), taking medication like herbal medicine and chemotherapy, thoracic aortic aneurysm and contraindications for magnetic resonance imaging (*e.g.* pacemakers, AICD, ferromagnetic implants and severe claustrophobia).

Data collection and CRP determination

Baseline characteristic data including age, sex, cardiovascular risk factors, prior diseases and medications, were reviewed from the patients and medical records. Blood sampling was drawn before starting MRI process, then immediately transferred to a core laboratory. High sensitive CRP (hs-CRP) level was measured by a method of an immune nephleometry. Using the quantitative sandwich enzyme immunoassay technique, the microplate was precoated by polyclonal antibodies directed against CRP. Normal assay value ranged from 0.175 to 100 mg/l. The coefficients of variation of lipid less than 5% and CRP were 2.3-4.4% and 2.5-5.74% for intra-assay and inter-assay variation.

Cardiac MRI study was performed using with a commercial 1.5 T Phillips Achieva XR scanner (Phillips Medical System, Best, the Netherlands). Cardiac axis was located by electrocardiogram-triggered non breath hold blackblood single shot sequentive 100 slides. Imaging parameters were as followed; Echo time (TE) 20 ms, repetitive time (TR) 1800 msec, refocusing flip angle 90°, slide thickness 8 mm, field of view in x axis (FOVx) 240-360 mm, field of view in y axis (FOVy) 250-280 mm, typical matrix size 118 *115 mm, typical acquired spatial resolution 1.59-1.86 *2.17-2.43 mm.

PWV was assessed using velocity encoded MRI (VE-MRI) technique as the through plane flow in the mid ascending and descending aorta at the level of pulmonary trunk. The scanning parameters were Echo time (TE) 3.6 ms, repetitive time (TR) 5.3 msec, refocusing flip angle 12°, slide thickness 8 mm, Field of view in x axis (FOVx) 320mm, Field of view in y axis (FOVy) 270 mm, typical matrix size 160 *132 mm, typical acquired spatial resolution 2.0*2.04 mm, temporal resolution 10 - 12 ms, and velocity encoding 170 cm/s.

Imaging analysis

Using cardiovascular imaging software (Extended workspace), the contours of mid ascending and descending aorta were manually drawn to obtain the flow in (m/sec) these 2 locations in all phases of the cardiac cycle. Therefore the corresponding flow time curve was generated. The arrival time of pulse wave was determined as the point of interception of linear extrapolation of baseline and steep early systolic stage. The aortic path length was measured by multiplanar reconstruction of axial halt fourier acquisition from steady stage image. Regarding reconstructed sagittal view, the path length was drawn as the centerline from the levels of the mid ascending aorta to the mid descending aorta, corresponding to the same level as VE-MRI image obtained. PWV between mid ascending and descending aorta was determined by the following formula:

$PWV = \Delta x/\Delta T$ (m/sec)

When = Δx represented the length of aortic path between the mid ascending and mid descending aorta and ΔT reflected the time delay between the arrival of the foot of pulse wave at these 2 levels[6].

Inter-observer and Intra-observer variability

In order to assess inter- and intra-observer variability, 20 patients were randomly selected in order to measure inter-observer and intra-observer variability by the same observer 4 weeks after initial analysis and by a second independent observer who was blinded to the initial results.

Statistic analysis

All statistical analysis were performed under the statistical software program (SPSS version 16, Chicago, Illinois, USA). Continuous data was expressed as mean and SD for normally distributed data or median, and Pearson correlation for normal distributed data or Spearman correlation for non-normally distributed data whereas dichotomous data were expressed as percentage. The associations between hs-CRP and PWV and hs-CRP and age were determined using Pearson correlation technique. The analysis of covariance was applied to analyze the correlation between hs-CRP and PWV, adjusting for age. Intra-observer and inter-observer variability of PWV were performed using the Bland-Altman Method. A p-value of < 0.05 was determined to be statistically significant.

Results

Baseline characteristics

The authors prospectively evaluated 90 patients undergoing cardiac MRI for suspected CAD. The baseline characteristics were shown in Table 1. Mean age was 68.05 $\pm$ 10.13 years, with 48 male (53.3%). Hemodynamic data revealed mean heart rate of 78 $\pm$ 12.4 bpm, systolic blood pressure of 135.11 $\pm$ 18.28 mmHg, diastolic blood pressure of 102.5 $\pm$ 11.12 mmHg. Ejection fraction of 58.46 $\pm$ 20.3% and pulse pressure

of 63.3 ± 17.74 mmHg. Two main parameters were hs-CRP (mean 7.62, SD 28.59 mg/L) and PWV (mean 11.43, SD 5.13 m/sec).

PWV and hs-CRP

PWV could be assessed in all patients with good quality. There was a significant correlation between PWV and hs-CRP (r = 0.251, p = 0.017). Further, the relationship between PWV and age (r = 0.244, p = 0.02) was significantly demonstrated. After adjustment by age, the association between PWV and hs-CRP remained significant (r = 0.223, p = 0.033) as shown in Fig. 1 and 2.

Reproducibility of PWV measurement

There was good reproducibility of inter-observer and intra-observer measurement of PWV. The mean PWV ± SD value was 11.43 ± 5.13 m/sec. and 10.95 ± 6.40 m/sec. (r = 0.657) for an initial analysis and 4 weeks after by the first observer, accordingly and 11.40 ± 6.80 m/sec. (r = 0.771) by the second observer. By Bland-Altman method, mean difference of 2 intra-observer measurements was 0.771 m/sec (p = 0.001) and inter observer mean difference were 0.657 m/sec (p = 0.008), respectively as shown in Fig. 3 and 4.

Discussion

The present study demonstrated the association between abnormal aortic stiffness and elevated hs-CRP. This is the pioneer effort designed to assess the correlation between abnormal aortic stiffness, represented as PWV using cardiac MRI and hs-CRP level. Further, both promising cardiovascular risks, abnormal aortic property and elevated vascular inflammatory markers, may provide a superior risk stratification of coronary artery diseases.

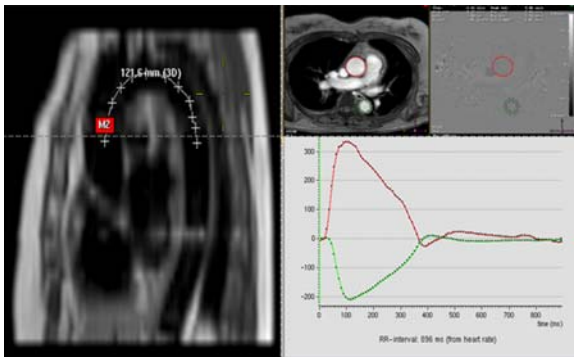

Fig. 1 Assessment of time delay and aortic path length between mid ascending and descending aorta (Left). Measurement of aortic path length from a multi planar reconstructed oblique sagittal view (Upper). VE-MRI at mid-ascending (red circles) and mid-descending thoracic aorta (green circles) **(**Below). Measurement of flow at measurement at mid-ascending (red line) and mid-descending thoracic aorta (green line).

hs-CRP

There was one large meta analysis of 14 studies from 1993-2004 including more than 12,000 patients. In comparing participants in the top third with those in the last third of baseline C-reactive protein, it reported odds ratio for coronary vascular disease of 2.0 (95% CI, 1.6 to 2.5) after adjustment for baseline values. Moreover, one of these studies demonstrated that even in high risk CAD patients, who had angina but negative cardiac enzyme, a rise of C-reactive protein was associated with cardiac outcomes (p = 0.001 for CRP in upper quartile and p = 0.002 for CRP ≥ 1 mg/L)[7].

Aortic stiffness

Recent knowledge had revealed increasing evidence to suggest a role of aortic stiffness, represented by PWV, in relation to atherosclerotic process. The meta analysis of 17 studies in 2009 recognized the end point of cardiovascular outcomes, in 15,877 patients with 7.7 years follow-up. The result revealed relative risk of total CV events, CV mortality and all cause mortality of 2.26 (95% CI 1.89 to 2.70, 14 studies), 2.02 (95% CI: 1.68 to 2.42, 10 studies), and 1.90 (95% CI: 1.61 to 2.24, 11 studies), respectively, for high versus low aortic PWV subjects. Relative risk increased14%, 15%, and 15% in total CV events, CV

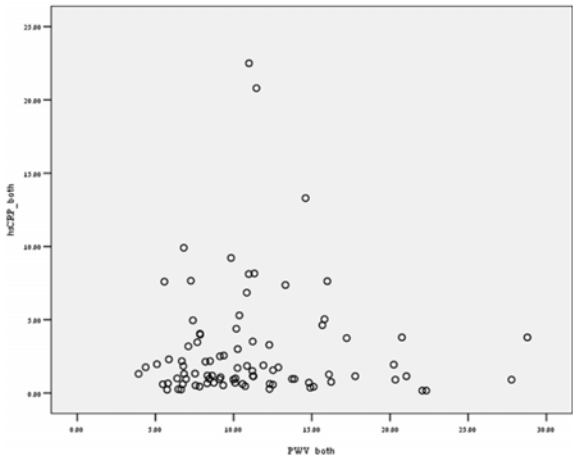

Fig. 2 Scatter plot of correlation of PWV and hs-CRP (r = 0.251, p = 0.017)

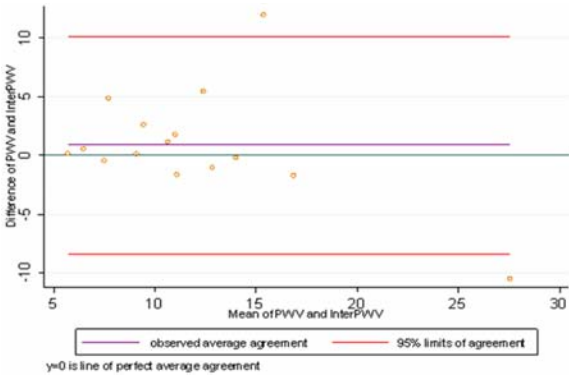

Fig. 3 Bland Altman plot of inter-observer reproducibility of PWV

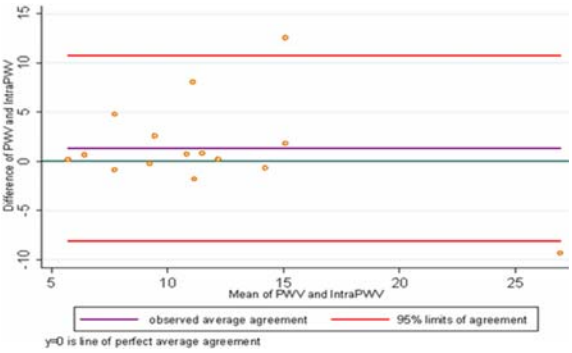

Fig. 4 Bland Altman plot of intra-observer reproducibility of PWV

mortality and all-cause mortality, accordingly. An increase in aortic PWV by 1 SD was associated with respective increase of 47%, 47%, and 42%[3].

Although many noninvasive indices for aortic stiffness have been proposed such as PWV, aortic distensibility by various modalities, PWV is good index of aortic stiffness owing to absence of central pressure assumption, along with high reproducibility.

Various modalities have been used for the assessment of PWV, such as cardiac MRI and Doppler ultrasound. Nevertheless, some limitations of Doppler ultrasound existed including observer dependent, inadequate techniques in obese patients and the need of aortic length assumption from body surface. Using aortic distensibility, Limitation included the need of central pressure estimation by sphygmomanometer, thus easily made technical errors. PWV assessed by cardiac MRI may be a better technique to reduce technical error by the ability to display the anatomy of vessels in any plane and to detect flow in any direction by velocity-encoded sequence. Importantly, PWV by VE-MRI does not limit researchers to geometrical assumption and knowledge of central arterial pressure.

Relationship between hs-CRP and aortic stiffness

A few prior studies have demonstrated the association between inflammatory markers (either CRP or hs-CRP) and abnormal aortic property (defined as either PWV or aortic distensibility)[8,9]. The same correlation between hs-CRP and PWV has been established in the present study. Moreover, the present study used VE-MRI, which is proposed as a promising tool for the assessment of aortic stiffness. This association could be explained as an independent pathogenesis for atherosclerosis, or in contrast, vascular inflammation as reflected by elevated hs-CRP, which would cause abnormality in wall property as represented by abnormal stiffness. These 2 mechanisms have been investigated as predictors for CAD. Combination of these 2 distinct mechanisms (inflammation and wall stiffness) may allow us to achieve more superior risk stratification than the traditional risk factors used nowadays.

Clinical implication and future direction

Abnormality in these 2 markers could accentuate a process of atherosclerosis. Using both distinct markers as predictors of future CAD may provide a better risk stratification than conventional risk factors. However, this aspect needs further study in order to answer this hypothesis. Moreover, combination of these 2 markers potentially leads to a superior prognosticator, as compared to a mere individual marker.

Study limitations

The present study chose hs-CRP as an inflammatory marker; nonetheless this marker has lack of specificity. hs-CRP could be abnormal in conditions, other than vascular inflammation, such as active infection, other systemic inflammation, or reduced renal function[10]. The authors attenuate this non-specificity by excluding these conditions with thoroughly detailed history and physical examination.

Aortic stiffness is a relatively novel marker for cardiovascular outcome, still without well-established normal cut-off and standard investigation. Nevertheless, the authors decided to use PWV assessed by MRI for that could be used without any geometrical and central arterial pressure assumption.

Conclusion

The correlation of an inflammatory marker, hs-

Table 1. Baseline characteristics of 90 patients

Parameters	
Age (years)	68.05 (10.13)
Male	48 (53.3)
Height (cm.)	157.73 (9.67)
Weight (kg.)	65.12 (11.71)
DM	44 (48.8)
HT	70 (77.8)
Dyslipidemia	57 (63.3)
Smoking	12 (13.3)
SBP (mmHg)	135.11 (18.28)
DBP (mmHg)	102.5 (11.12)
HR (bpm)	78 (12.4)
LVEF (%)	58.46 (20.3)

Continuous data were shown as mean (SD). Categorical data were shown as number (percentage) cm; centimeter, kg; kilo gram, DM; diabetes mellitus, HT; hypertension, SBP; sys tolic blood pressure, DBP; diastolic blood pressure, HR; heart rate, bpm; beat per minute, LVEF; left ventricular ejec tion fraction

CRP and abnormal aortic property, PWV, has been established in the present study, using a concept of MRI. This potentially reflects an inflammation as a contributor to an abnormal aortic wall property. The application of these 2 markers for clinical situation, such as improvement of risk stratification and prognosis, warrants further study.

Acknowledgement

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Potential conflicts of interest

None.

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การศึกษาความสัมพันธ์ของค่า C-reactive protein กับ ความแข็งของหลอดเลือดแดง ด้วยการตรวจด้วยเอกซเรย์คลื่นแม่เหล็กไฟฟ้าในผู้ป่วยที่เข้ารับการรักษาในโรงพยาบาลศิริราช

ภัทรภร ศรีรัตนา, ธนัญญา บุณยศิรินันท์

***ภูมิหลัง**: CRP เป็นค่าที่บ่งบอกถึงภาวะที่มีการอักเสบภายในร่างกายอย่างไม่จำเพาะเจาะจง ส่วนภาวะการแข็งของหลอดเลือดแดง (aortic stiffness) เป็นการสะท้อนถึงความสามารถในการยืดหยุ่นของหลอดเลือด ทั้งสองตัวแปรมีรายงานที่กล่าวถึงความสัมพันธ์กับปัจจัยเสี่ยงในการเกิดภาวะโรคหัวใจ อย่างไรก็ตามยังมีข้อมูลไม่มากที่กล่าวถึงความสัมพันธ์ดังกล่าวในการเป็นดัชนีชี้วัดภาวะหลอดเลือดหัวใจตีบ*

***วัตถุประสงค์**: เพื่อทำการศึกษาในผู้ป่วยที่เข้ารับการตรวจด้วยเครื่องเอกซเรย์คลื่นแม่เหล็กไฟฟ้า เนื่องจากสงสัยภาวะหลอดเลือดหัวใจตีบในโรงพยาบาลศิริราช เพื่อประเมินโรคหลอดเลือดหัวใจตีบ ว่าจะมีความสัมพันธ์ของภาวะการแข็งของหลอดเลือด ต่อค่า C reactive protein หรือไม่เพื่อเป็นการหาคำตอบในสมมุติฐานว่าการอักเสบมีผลต่อการแข็งตัวของหลอดเลือดในกลุ่มประชากรดังกล่าวหรือไม่ อันอาจจะนำไปสู่การพยากรณ์การเกิดโรคในอนาคตต่อไป*

***วัสดุและวิธีการ**: ผู้ป่วยที่เข้ารับการตรวจด้วยเครื่องเอกซเรย์คลื่นแม่เหล็กไฟฟ้าจำนวน 90 คน โดยภาวะการแข็งตัวของหลอดเลือดประเมินจากความเร็วของการไหลของเลือด (pulse wave velocity, PWV) โดยการประเมินจากสัดส่วนระหว่างระยะจากส่วนกลางของหลอดเลือดแดงใหญ่ส่วน ascending และdescending กับ เวลาที่ใช้จากระดับล่างของ pulse wave ถึงระดับที่วัด โดยการใช้ภาพจากเครื่องเอกซเรย์คลื่นแม่เหล็กไฟฟ้า เทียบกับค่า hs-CRP*

***ผลการศึกษา**: ผู้ป่วยที่ได้รับการตรวจด้วยเครื่องเอกซเรย์คลื่นแม่เหล็กไฟฟ้าหัวใจจำนวน 90 คน แบ่งเป็น หญิง 42 คน ชาย 48 คน มีการบีบตัว ของหัวใจด้านซ้ายเฉลี่ย 58.46 $\pm$ 20.3% พบว่ามีค่าเฉลี่ยของ hs-CRP 7.62 $\pm$ 28.59 มก./ลิตร และค่าเฉลี่ยของ PWV 11.43 $\pm$ 5.13 เมตร/วินาที และมีความ สัมพันธ์กันระหว่าง hs-CRP และ PWV อย่างมีนัยสำคัญ ($r = 0.251$, p-value = 0.017) และ ความสัมพันธ์ของ PWV เทียบกับอายุพบว่ามีความสัมพันธ์กันอย่างมีนัยสำคัญเช่นกัน ($r = 0.244$, p-value = 0.02)*

***สรุป**: มีความสัมพันธ์ของค่าการแข็งตัวของหลอดเลือดแดง และ hs-CRP อย่างมีนัยสำคัญในระดับปานกลาง*