

# Effects of Intravenous PD 123319 on Haemodynamic and Arterial Stiffness Indices in Healthy Volunteers

Divina G Brillante,<sup>†</sup> Martina T Jobstone,<sup>\*</sup> Laurence G Howes<sup>‡</sup>

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<sup>†</sup> Department of Medicine  
St. George Clinical School, University of New South Wales, Kogarah NSW 2217 Australia

<sup>\*</sup> Department of Nuclear Medicine, St. George Hospital, Kogarah NSW 2217 Australia

<sup>‡</sup> Department of Pharmacology and Therapeutics  
Gold Coast Hospital, Griffith University, Southport, QLD 4215 Australia

Correspondence to:  
Professor Laurence G Howes,  
Department of Cardiology,  
Level 9, Gold Coast Hospital  
Nerang St, Southport  
QLD 4215 Australia  
Tel: +61 7 5571 8979  
Fax: +61 7 5571 8696  
E-mail: laurie\_howes@health.qld.gov.au

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## Abstract

Relatively little is known about the functional expression of cardiovascular angiotensin type 2 (AT<sub>2</sub>)-receptors in healthy young adult humans. We performed a randomised, placebo-controlled crossover study of the effects of intravenous administration of the selective AT<sub>2</sub>-receptor antagonist PD 123319 on haemodynamics and arterial stiffness in normal volunteers.

Sixteen normal subjects aged 29.9 ± 13.8 years (range 18–30 years) received an intravenous infusion of PD 123319 (10 mcg/minute for 5 minutes) and placebo, separated by one week. Haemodynamics (cardiac index, stroke index and systemic vascular resistance) were measured non-invasively using a BioZ.com thoracic impedance detection system. Blood pressure was measured from an arm cuff using oscillometry. Stiffness index, a measure of arterial stiffness, was measured using a PulseTrace recorder.

No significant changes in blood pressure (p=0.92), cardiac index (p=0.52), stroke index (p=0.61), systemic vascular resistance index (p=0.32) or stiffness index (p=0.57) was demonstrated following PD 123319 infusion, compared with placebo.

The results of this study do not support the functional presence of cardiovascular AT<sub>2</sub>-receptors that mediate acute haemodynamic effects in healthy young adults. It remains possible that higher doses of PD 123319 may be required to demonstrate functional cardiovascular AT<sub>2</sub>-receptors in this population, if they are present.

## Introduction

The renin-angiotensin system plays a significant role in the development of cardiovascular disease. Its effector hormone, angiotensin (Ang II), acts on two principal receptor subtypes, AT<sub>1</sub> and AT<sub>2</sub>-receptors. The AT<sub>1</sub>-receptor mediates most of the potentially harmful effects of Ang II, including vasoconstriction, salt and water retention and endothelial dysfunction.<sup>1–3</sup> Less is known about the functional significance of the AT<sub>2</sub>-receptor. It is known to be expressed ubiquitously in the foetus, but disappears rapidly in most tissues after birth.<sup>1,2</sup> Vascular AT<sub>2</sub>-receptors are hypothesised

to reappear following vascular damage and to mediate predominantly opposing effects to those of the AT<sub>1</sub>-receptor.<sup>1,2</sup> A previous study by our department involving elderly women receiving the AT<sub>1</sub>-receptor blocker, candesartan, demonstrated an increase in forearm vascular resistance (FVR) in response to intrabrachial arterial infusion of the selective AT<sub>2</sub>-receptor antagonist, PD 123319, suggesting a functional role for vascular AT<sub>2</sub>-receptors.<sup>4</sup> A subsequent study in healthy volunteers, however, showed no alteration in FVR, in response to intra-arterial PD 123319, regardless of the presence or absence of intercurrent AT<sub>1</sub>-receptor blockade with telmisartan.<sup>5</sup> Of interest, the results of the latter study suggested that PD 123319 may increase mean arterial pressure.

In recent years, it has been reported that measures of arterial stiffness are important predictors of cardiovascular morbidity and mortality, and that AT<sub>1</sub>-receptors play a role in the regulation of large artery compliance.<sup>3,6,7</sup> The role of AT<sub>2</sub>-receptors in this regard is unknown. In the present study, we investigated the effect of intravenous PD 123319 on mean arterial pressure, blood pressure, cardiac index, systemic vascular resistance index and arterial stiffness index in healthy volunteers.

## Materials and Methods

The study was performed at the Department of Medicine, St George Hospital, Australia. Approval to perform the study was obtained from the South Eastern Sydney Area Health Service Research and Ethics Committee.

## Subjects

Subjects were recruited through approved public advertisements. Volunteers attended a screening visit to assess their suitability to participate in the study. They were considered eligible to participate if they fulfilled the following criteria: age between 18 and 55 years, able to give written informed consent, non-smoker, systolic blood pressure < 150 mmHg, diastolic blood pressure < 90 mmHg, absence of cardiovascular disease, BMI < 30 kg/m<sup>2</sup>, not receiving vasoactive medications (including hormone replacement therapy, statins, antihypertensives or bronchodilators), total cholesterol < 7.5 mmol/L, TG

< 4.0 mmol/L, non-diabetic, alcohol consumption < 20g per day, creatinine < 120 mmol/L and haemoglobin > 120 g/L. Women of child-bearing potential were screened with a urinary pregnancy test, to exclude the possibility of pregnancy.

### Study Design

This was a randomised, double-blind, placebo-controlled, crossover study. After the screening visit, a hospital scientist from the Department of Nuclear Medicine was notified of the subject's consent to participation. The scientist randomised subjects to receive PD 123319 (diluted in normal saline and infused at 2 mL/minute at a concentration of 10 mcg/minute) or placebo (saline solution at 2 mL/minute). A process of blocked randomisation (block size 4) was used, and the block factor or block size was unknown to the investigator.

PD 123319 was obtained from Sigma-Aldrich Chemical Company (Sydney, Australia), with a stated purity of greater than 97%. Solutions were prepared aseptically by dissolving PD 123319 in sterile water to obtain a pre-determined PD 123319 concentration. Aliquots were dispensed in autoclaved vials and then freeze-dried. Ten per cent of the samples were randomly selected and sent for sterility and pyrogenicity testing, and were found to be sterile and pyrogen-free. The solutions were received in a pre-loaded syringe on the day of each study visit. The investigators were blinded to the identity of the solution throughout the study.

The subjects attended the clinic in the morning after an overnight fast and having abstained from alcohol and caffeinated foods and beverages for 24 hours. They were requested to rest supine for 30 minutes in a temperature-controlled room ( $27 \pm 1^\circ \text{C}$ ) to allow acclimatisation. A 22G intravenous cannula was then inserted into a left forearm vein for infusion of placebo or PD 123319. Arterial stiffness indices were measured using a previously validated portable photoplethysmograph (Micro Medical PulseTrace, Kent, UK),<sup>8-15</sup> which collects digital volume pulse data from a probe placed on the left index finger. In-built software calculated measurements of arterial stiffness index (SI) after entry of the subject's demographic data. Cardiac index (CI), stroke index (ZI), systemic vascular resistance index (SVRI), blood pressure, and mean arterial pressure (MAP) were measured using a thoracic electrical bioimpedance monitor (Cardiodynamics International Corporation, San Diego, CA. BioZ system) with an in-built oscillometric sphygmomanometer. The accuracy and reproducibility of this device has been investigated and validated.<sup>16-20</sup> For both arterial stiffness and haemodynamic parameters, baseline recordings were measured at one-minute intervals for a total of 5 minutes. Values were averaged to give a mean baseline result. Placebo or PD 123319 infusion was then commenced, and recordings made at one-minute intervals for five minutes,

after which the infusion was stopped. Values were averaged, and the means compared with the mean baseline values. Arterial stiffness indices and haemodynamic measurements continued after cessation of the infusion until values returned to baseline.

The subjects returned after a one-week wash out period for the second treatment phase of the study. Those who received intravenous PD 123319 during their first study visit were given intravenous placebo and vice versa. The rest of the protocol is as outlined above.

### Statistical Analysis

Results are given as the mean  $\pm$  standard deviation. Statistical comparisons with student's paired *t*-test were performed using STATISTICA 6.0 software. The primary endpoint of the study was the difference in the mean percentage change in AT<sub>2</sub>-receptor-mediated responses from baseline between active and placebo groups. Based on previous studies by the host laboratory, a study of 16 subjects was expected to give 80% statistical power to detect a difference of >20% in responsiveness (two-tailed alpha of  $p < 0.05$ ). Changes smaller than this were considered not to be clinically relevant.

The intra-individual reproducibility of data for each parameter was assessed by calculating the co-efficient of variation of the five baseline readings during each study day in each subject. The co-efficients of variation (CV) were averaged and presented as the mean CV for each study day. Interday reproducibility was assessed by calculating the CV of the difference in mean baseline measurements during each study day.

### Results

Sixteen Caucasian subjects were recruited, aged between 18 and 55 ( $29.9 \pm 13.8$  years). Nine subjects were younger than 30 years, seven were male. All were non-diabetic, non-smokers and were not taking any medications. All of the subjects completed the study. No adverse effects were reported.

The baseline characteristics of the subjects are outlined in Table 1.

The results of the mean percentage change in values for systolic blood pressure (SBP), MAP, CI, SVRI, ZI and SI from baseline to infusion of placebo (P) or PD 123319 (A) are presented in Table 2.

Comparison of the mean percentage change during placebo and PD 123319 infusion using the student's paired *t*-test did not demonstrate any statistically significant difference between the two infusions for any of the parameters.

Table 3 shows the co-efficient of variation of the difference in mean baseline measurements

**Table 1**  
Subject demographics and baseline measurements. The results are presented as mean ± SD.

Demographics and Baseline Measurements	Mean ± SD
No. of patients	16
Age (years)	29.9 ± 13.8
Gender	
Female	9
Male	7
BMI (kg/m <sup>2</sup> )	23.4 ± 2.5
Cholesterol (mmol/L)	4.26 ± 1.0
Triglycerides (mmol/L)	1.06 ± 0.53
Creatinine (mmol/L)	0.07 ± 0.01
Haemoglobin (g/L)	134 ± 16
SBP (mmHg)	109 ± 2.8
MAP (mmHg)	79.5 ± 2.6
CI (L/minute/m)	3.2 ± 0.1
SVRI (dyne s m)	1853.1 ± 106.1
ZI (mL/m)	49.4 ± 1.4
Stiffness Index (m/s)	6.3 ± 0.3

SBP = systolic blood pressure; MAP = mean arterial pressure; CI = cardiac index; SVRI = systemic vascular resistance index; ZI = stroke index.

**Table 2**  
Mean percentage change of value from baseline to infusion of placebo or PD 123319.

Parameter	Placebo Infusion (Mean % change from Baseline ± Standard Deviation)	PD 123319 Infusion (Mean % change from Baseline ± Standard Deviation)	p-value
SBP	0.00 ± 0.04	0.01 ± 0.05	0.72
MAP	-0.00 ± 0.03	-0.01 ± 0.07	0.92
CI	-0.01 ± 0.05	0.01 ± 0.04	0.51
SVRI	-0.01 ± 0.05	-0.02 ± 0.07	0.32
ZI	-0.01 ± 0.03	0.01 ± 0.06	0.61
SI	0.00 ± 0.04	0.02 ± 0.08	0.57

between each study day, demonstrating good inter-day reproducibility.

Intraindividual CV for each measured parameter was less than 10%, indicating good intraindividual reproducibility of data.

**Table 3**  
Co-efficient of variation (CV) for difference in baseline means between study day 1 and study day 2.

Haemodynamic Parameter	Co-efficient of Variation (CV)
SBP	3% ± 0.02
MAP	6% ± 0.03
CI	10% ± 0.09
SVRI	16% ± 0.15
ZI	8% ± 0.06
SI	7% ± 0.06

**Table 4**  
Mean intraindividual co-efficient of variation during each study day.

Parameter	Day 1 Infusion Mean CV	Day 2 Infusion Mean CV
SBP	2.57%	3.20%
MAP	3.27%	2.26%
CI	4.16%	4.93%
SVRI	5.82%	6.29%
ZI	2.88%	4.31%
SI	4.92%	5.26%

### Discussion

There is evidence that AT<sub>2</sub>-receptors are up-regulated in diseased cardiovascular beds, and that they may play a cardioprotective role in these circumstances.<sup>1,2</sup> This study did not demonstrate a significant alteration in blood pressure, MAP, CI, SVRI, ZI and arterial stiffness index after intravenous administration of PD 123319 (10 mcg/minute) in healthy volunteers. The results of this study therefore, do not support the presence of functional cardiovascular AT<sub>2</sub>-receptors in healthy individuals.

Our department has performed a number of studies examining forearm blood flow (FBF) responses to intra-brachial arterial infusion of the selective AT<sub>2</sub>-receptor antagonist, PD 123319, in different population subgroups. A study involving women aged > 65 years with no known cardiovascular disease, and who were not receiving hormone replacement therapy, demonstrated a significant reduction in FBF in response to intra-arterial PD 123319 in the presence of AT<sub>1</sub>-receptor blockade with candesartan, suggesting the functional presence of AT<sub>2</sub>-receptors.<sup>4</sup> In contrast, a study involving healthy young males (26–28 years) found no change in FBF responses to increasing doses of Ang II (0–32 ng/minute) and PD 123319 (8 mcg/minute).<sup>21</sup> A subsequent study involving healthy young male and female volunteers demonstrated no change in forearm

blood flow in response to intra-arterial PD 123319 (10 mcg/minute), irrespective of whether or not they were receiving chronic telmisartan therapy.<sup>22</sup> However, a significant increase in mean arterial pressure was observed ( $p=0.003$ ) during intra-brachial arterial infusion of PD 123319 in the latter study. We postulated that this might reflect a systemic effect of PD 123319 on vascular beds other than the forearm vascular bed.

There are several significant differences between the present study and the previous study which demonstrated a significant increase in mean arterial pressure with intra-brachial arterial PD 123319 infusion. Firstly, different methods were used to measure blood pressure at different sites. In the previous study, blood pressure was measured using a Finapres (Ohmeda, Eaglewood, Colorado, USA) recorder, which uses digital photoplethysmography to measure beat-to-beat blood pressure from the index finger; readings of mean arterial pressure are calculated from the arterial waveform by in-built software.<sup>19,20</sup> In the present study, an oscillometric sphygmomanometer connected to the BioZ device was used for the measurement of blood pressure parameters. Secondly, the previous study was not placebo-controlled for PD 123319 infusion, which may have resulted in time effects on blood pressure. Finally, the population in the previous study were younger (18–31 years, compared with 18–55 years in the present study).

A limitation of this study was that only a single dose of PD 123319 was used. To our knowledge, this is the first time PD 123319 has been administered intravenously to humans. The dose of 10 mcg/minute for five minutes was used based on our previous studies which produced a significant increase in mean arterial pressure using the same dose administered intra-arterially. Dose-response studies are required to investigate possible cardiovascular effects of PD 123319 at higher doses.

The method of measuring haemodynamic parameters using the BioZ device (Cardiodynamics International Corporation, San Diego, CA. BioZ system) produced highly reproducible data in this study. Similarly, measurement of arterial stiffness index using the Micro Medical Pulse Trace (Kent, UK) demonstrated good reproducibility.

The intravenous infusion of PD 123319 10 mcg/minute was well tolerated, and without adverse effects.

## Conclusion

In conclusion, this study demonstrated that intravenous infusion of the selective AT<sub>2</sub>-receptor antagonist, PD 123319, in healthy individuals, did not produce any significant effect on mean arterial blood pressure, CI, SVRI, reflective index and arterial stiffness index. Further studies on the effect of intravenous PD 123319 in patients

with cardiovascular risk factors or cardiovascular disease may better demonstrate the functional role of the AT<sub>2</sub>-receptor, and confirm the suggestion that they become functionally expressed in abnormal cardiovascular tissues.

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