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# 学位論文

学位論文名

Opposing responses of the calcium channel blocker nicardipine  
to vascular stiffness in the elastic and muscular arteries  
in rabbits

(カルシウム拮抗薬ニカルジピン投与に対するウサギ  
弾性動脈と筋性動脈の硬さは相反的応答を示す)

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## 概要

【背景】動脈壁の硬さを正確に計測することは動脈硬化などの診断に非常に重要であり、その指標として脈波速度(PWV)が広く用いられているが、測定時血圧に大きく依存するため、血管壁本来の硬さが正確に反映されない。一方、心臓－足首血管指数(CAVI)は血圧に依存しない血管壁の硬さの指標として開発され、近年国内外の医療機関で普及しつつある。しかしながら、CAVI は心臓から前脛骨、後脛骨動脈までの弾性動脈と筋性動脈を含む血管全体の硬さを反映する。循環系において、弾性動脈と筋性動脈は微細構築やその機能が異なるので、それぞれが降圧薬に対してどのように応答するかは明らかではない。

【目的】本研究では、CAVI 理論を弾性動脈と筋性動脈に適用することにより新しい動脈硬化指標 Beta を求めた。カルシウムチャンネル遮断薬であるニカルジピン投与に対する弾性動脈および筋性動脈の応答について Beta を指標に解析し、循環動態における両動脈の役割を検討した。

【方法】ペントバルビタール麻酔下で雄ウサギ 12 匹に 2 分間でニカルジピンを投与した際の大動脈起始部 (oA)、腹部大動脈遠位部(dA)、左大腿動脈(fA) における圧脈波および大動脈起始部の血流波形を同時記録した。Beta は次式  $\text{Beta} = 2\rho / \text{PP} \times \ln(\text{SBP} / \text{DBP}) \times \text{PWV}^2$  より求めた。但し、 $\rho$  : 血液密度、PP : 脈圧、SBP : 収縮期血圧および DBP : 拡張期血圧である。大動脈 Beta (aBeta)、総腸骨動脈～大腿動脈 Beta (ifBeta)および大動脈から大腿動脈までの Beta (aifBeta)はそれぞれに対応する aPWV、ifPWV および aifPWV から計算した。総末梢血管抵抗(TPR)は平均血圧(MAP) / 心拍出量(CO)として算出した。

【結果】SBP、DBP、MAP、TPR はニカルジピンの投与により有意に減少し、CO は有意に増加した。血圧の低下に伴い ifBeta は有意に減少したが、aBeta は有意に増加した。aifBeta には有意な変化を認めなかった。ifBeta は血圧に対して正相関を示したが、逆に aBeta は負相関を示した。aifBeta は有意な相関は示さなかった。

aPWV、ifPWV および aifPWV はいずれも血圧と有意な正相関が認められた。

【結語】ニカルジピン投与に対し、弾性動脈と筋性動脈は相反する応答を示すことが明らかになった。このメカニズムは今後解明されなければならないが、弾性動脈には血圧低下に関わらず、Ca<sup>2+</sup> イオン流入が関与しない未知の血管収縮メカニズムの存在が示唆された。今後、ヒトにおいても同様の結果が得られるかを検討する必要がある。

## **Abbreviation**

CAVI: Cardio-ankle vascular index

PWV: pulse wave velocity

aBeta: aorta Beta

ifBeta: iliac-femoral Beta

aifBeta: aortic-femoral Beta

aPWV: aortic PWV

ifPWV: iliac-femoral PWV

aifPWV: aortic-femoral PWV

oA: origin of the aorta

dA: distal end of the abdominal aorta

fA: left femoral artery

CO: cardiac output

TPR: total peripheral vascular resistance

HR: heart rate

BP: blood pressure

VSMCs: vascular smooth muscle cells

haPWV: heart-ankle pulse wave velocity

## Introduction

Arterial stiffness is mainly determined by the intrinsic properties of the artery, peripheral vascular tone, and cardiac function<sup>1, 2)</sup>. Peripheral vascular tone mainly affects blood pressure (BP) and cardiac output (CO)<sup>3)</sup>. It is thought that arterial stiffness is not only a marker of atherosclerosis but also plays a partial role in cardiovascular hemodynamics, such as vascular resistance<sup>2)</sup>.

The role of arterial stiffness in cardiovascular hemodynamics has not been elucidated as a proper index of arterial stiffness has not been contrived. Pulse wave velocity (PWV), a direct measure of arterial stiffness<sup>4, 5)</sup>, depends on the BP at the time of measurement<sup>6, 7)</sup>; the cardio-ankle vascular index (CAVI) has been developed based on the theory of the stiffness parameter  $\beta$ <sup>8, 9)</sup> and Bramwell–Hill's equation<sup>10)</sup>. CAVI reflects the overall stiffness from the origin of the aorta to the anterior and posterior tibial arteries, which contain the elastic and muscular arteries. The fine structure and function of the two types of artery are different<sup>11, 12)</sup>.

It is well demonstrated that the aorta mainly functions as an auxiliary pump, whereas the muscular arteries have a contraction–dilation function for transporting and distributing blood to the peripheral tissues. It is supposed that there is a cross-talk function between the aorta and muscular arteries and that the arterial stiffness of the two arteries is involved in this function. However, such a function had not been precisely evaluated, because an adequate index for the estimation of arterial stiffness had not been established.

To investigate the stiffness of the elastic (aorta) and muscular (iliac and femoral) arteries, we determined a stiffness index Beta by applying the CAVI theory to the whole aorta (aBeta) and iliac-femoral arteries (ifBeta). Katsuda et al.<sup>13)</sup> reported that BP decreased with the decrease in ifBeta and increase in aBeta when a

nonselective  $\alpha$ -adrenergic blocker, namely, phentolamine, was infused into rabbits. The mechanism and significance of the contradictory response remain unclear. One interpretation is that the increased aBeta might compensate for the decreased BP due to the dilation of the muscular arteries induced by the infusion of phentolamine. The question of whether this reciprocal response of arterial stiffness in the elastic and muscular arteries is induced by the infusion of  $\alpha$ -adrenergic blocker or other vasodilator drugs, such as a calcium channel blocker, arises.

## **Aim**

Voltage-dependent L-type calcium channels play a major role in  $\text{Ca}^{2+}$  influx into vascular smooth muscle cells (VSMCs) <sup>14, 15</sup>). Nicardipine, a voltage-dependent L-type and T-type calcium channel blocker, lowers BP by dilating the peripheral muscular arteries and arterioles <sup>16, 17</sup>). We investigated the change in the stiffness of the aorta and iliac-femoral arteries using aBeta and ifBeta in response to decreased BP induced by the administration of nicardipine to rabbits to elucidate the involvement of  $\text{Ca}^{2+}$  in the change in aBeta and ifBeta.

## **Methods**

### **1. Animals**

A total of 12 male Japanese white rabbits weighing  $3.39 \pm 0.19$  kg and aged 10–12 months (Japan Laboratory Animals, Inc., Tokyo, Japan) were used in the present study. They were individually reared in stainless wire cage in an air-conditioned breeding room at a room temperature of 20°C–26°C, a humidity level of about 50%–70%, and a 12L/12D cycle. In addition, they were given a commercial rabbit food (Labo R Grower, Nosan Corporation, Yokohama, Japan) at about 100 g/animal/day

and free access to water. The present study was approved by the Experimental Animal Committee of Fukushima Medical University and was conducted according to the Guidelines for Animal Care and Handling of the Japanese Association for Laboratory Animal Science.

## 2. Surgical procedure

Fig. 1 shows the schematic arrangement of the experimental setup. The surgical procedure was similar to that previously reported <sup>13)</sup>. The rabbits were anesthetized by intravenous administration of pentobarbital sodium (Somopentyl, Kyoritsu Seiyaku Corporation, Tokyo, Japan) at a dose of 30 mg/kg. Butorphanol tartrate (Vetorphal, Meiji Seika Pharma, Co., Ltd., Tokyo, Japan) was injected intramuscularly at a dose of 0.3 mg/kg for pain relief. The rabbit was fixed in supine and intubated trachea. Two catheter tip transducers (2.0 Fr, SPS-320, Millar Instruments, Inc., Huston, TX) were advanced to the origin of the aorta (oA) and distal end of the abdominal aorta (dA) through the left common carotid and right saphenous arteries, respectively. FISO catheter with a fiber optical pressure sensor at the tip (0.9 Fr, FPI-LS-10, FISO Technologies, Inc., Quebec, Canada) was introduced to the distal end of the left femoral artery (fA) through the left saphenous artery. An ultrasonic flow probe (6.0 mm, I.D.) was placed at the ascending aorta after carefully opening the chest under voluntary breezing to prevent injury to the pleura.

## 3. Measurement of Beta and PWV

Nicardipine hydrochloride (Sawai Pharmaceutical Co. Ltd., Osaka, Japan) was infused into the ear vein for 2 min using a syringe pump at a dose of 50 µg/kg/min. Pulse waves at the oA, dA, and fA and blood flow at the oA were simultaneously



measured using a polygraph (360 system, NEC Sanei Co., Ltd., Japan) and an ultrasonic blood flow meter (T206, Transonic Systems Inc., Ithaca, NY) and then recorded in a personal computer (PowerBook G4 M9691J/A, Apple Inc., Cupertino, CA, USA) using an analog-to-digital converter (PowerLab System 16/SP, AD Instruments, Inc., Sydney, Australia). After the measurement, the rabbits were euthanized with pentobarbital overdose. The distance between the two adjacent sensors at the catheter tip was accurately measured *in situ* with a string along the aorta and artery.

#### 4. Statistical analysis

Pulse and blood flow waves were analyzed for 50 successive cardiac cycles. The foot of the pressure wave was defined as the peak of the second derivative of the original pressure waves, as previously reported <sup>18)</sup>. PWV was calculated as the difference in the rising time of two pressure waves and the distance between two pressure sensors between the oA and dA (aortic PWV; aPWV), between the dA and fA (iliac-femoral PWV; ifPWV), and between the oA and fA (aortic-femoral PWV; aifPWV).

Arterial stiffness of the whole aorta (aBeta), iliac-femoral arteries (ifBeta), and whole aorta and iliac-femoral arteries (aifBeta) was measured by applying the CAVI theory. The CAVI is determined using the following formula <sup>19, 20)</sup>:

$$\text{CAVI} = a [2\rho \times \ln (\text{SBP} / \text{DBP}) / \text{PP} \times \text{PWV}^2] + b,$$

where  $\rho$ , SBP, DBP, and PP denote the blood density and systolic, diastolic, and pulse pressures, respectively, and “a” and “b” denote the undisclosed coefficients. Takahashi et al. <sup>21)</sup> defined heart-ankle Beta (ha $\beta$ ) as an index of the elasticity of the arteries without the coefficients “a” and “b” and demonstrated that there was no

difference in the significance or interpretation between the CAVI and  $\beta$  in epidemiological and clinical studies. Therefore, we took the coefficients “a” and “b” for “1” and “0,” respectively, in calculating Beta.

aBeta, ifBeta, and aifBeta were determined using aPWV, ifPWV, and aifPWV, respectively. SBP, DBP, and PP were the average values of oA and dA for aBeta, dA, and fA for ifBeta, and oA and fA for aifBeta.

Heart rate (HR) was measured from the pulse waves at the oA using a cardiometer. The mean arterial pressure (MAP) was calculated using a pulse wave passed through a low-pass filter at 2.5 s. Total peripheral vascular resistance (TPR) was measured by dividing the cardiac output (CO) by the MAP.

These variables were determined before and after nicardipine infusion every 1 min for 5 min. The data were tested *via* one-way analysis of variance (ANOVA). When a significant difference was observed in the ANOVA, a *post hoc* test was conducted using Scheffe’s multiple comparisons test. We calculated Pearson’s correlation coefficient for each Beta and PWV against SBP, DBP, MAP, CO, and TPR, and the correlation coefficient was tested using the F-test. The significance level was set to  $p = 0.05$ .

## Results

### 1. Time-dependent changes in cardiovascular variables, PWV, and Beta during the infusion of nicardipine

Fig. 2 presents the time-dependent changes in SBP and DBP at the oA, dA, and fA (A); HR and CO (B); MAP and TPR (C); aBeta, ifBeta, and aifBeta (D); and aPWV, ifPWV, and aifPWV (E) during nicardipine infusion. SBP and DBP significantly decreased at the oA, dA, and fA due to the infusion of nicardipine. Moreover, CO

increased significantly, whereas the MAP and TPR decreased significantly during the infusion of nicardipine. HR demonstrated a slight but significant decrease 3–5 min after the administration. We investigated the changes in aBeta, ifBeta, and aifBeta concomitant with the decrease in BP during nicardipine infusion. ifBeta decreased significantly, whereas aBeta increased. aifBeta, which corresponds approximately to the CAVI, did not exhibit a significant change. aPWV, ifPWV, and aifPWV decreased significantly in a pressure-dependent manner during the infusion of nicardipine.

## 2. Relationship of BP with Beta and PWV

Fig. 3 presents the correlation between Beta and SBP (A), Beta and MAP (C), Beta and DBP (E), PWV and SBP (B), PWV and MAP (D), and PWV and DBP (F) during the infusion of nicardipine. aBeta was significantly negatively correlated with SBP, MAP, and DBP, whereas ifBeta significantly positively correlated with SBP, MAP, and DBP. aifBeta did not demonstrate a significant correlation with SBP; however, it exhibited a significant negative correlation with MAP and DBP. aPWV, ifPWV, and aifPWV showed a significant positive correlation with SBP, MAP, and DBP during the infusion of nicardipine.

## 3. Relationship of Beta with CO and TPR and PWV with CO and TPR

Fig. 4 presents the correlation between Beta and CO (A), PWV and CO (B), Beta and TPR (C), and PWV and TPR (D) during the infusion of nicardipine. aBeta and aifBeta did not exhibit a significant correlation with CO, whereas ifBeta demonstrated a significant negative correlation with CO. aBeta had a significant negative correlation with TPR, whereas ifBeta positively correlated with TPR. No significant correlation was observed between aifBeta and TPR. aPWV, ifPWV, and

aifPWV significantly negatively correlated with CO, whereas aPWV, ifPWV, and aifPWV showed a significant positive correlation with TPR.

## Discussion

Nicardipine, a calcium channel blocker, relaxes the VSMCs of the muscular arteries and arterioles by blocking L-type and T-type  $\text{Ca}^{2+}$  channels<sup>16, 17)</sup>, which reduces peripheral vascular resistance, leading to a decrease in BP<sup>22)</sup>. Nicardipine also dilates the coronary artery<sup>23)</sup>, which results in an improved left ventricular function without producing any negative inotropic effects<sup>24)</sup>. The  $\alpha_1$  subunit of the vascular smooth muscle  $\text{Ca}^{2+}$  channel has a higher affinity for dihydropyridine drugs than the  $\alpha_1$  subunit of the heart. The selectivity of the action of nicardipine on the vascular smooth muscle is more than 10,000 times that on the cardiac muscle<sup>25)</sup>.

In this study, we observed a significant decrease in TPR, BP, and HR and a significant increase in CO during nicardipine infusion. These findings are almost consistent with those of other investigators, except that with regard to HR<sup>22, 24)</sup>. Satoh<sup>26)</sup> also reported that a high dose of nicardipine inhibited tachycardia induced by sympathetic nerve stimulation mainly by suppressing slow inward  $\text{Ca}^{2+}$  currents. The significant increase in CO is considered to be mainly caused by the decrease in peripheral vascular resistance.

aPWV, ifPWV, and aifPWV demonstrated a significant decrease concomitant with the decrease in BP during the infusion of nicardipine as well as a significant positive correlation with SBP, MAP, and DBP. PWV has been shown to change depending on BP at the time of measurement. Thus, it was difficult to determine whether decreased PWV was derived from a decrease in intrinsic stiffness or just by accompanying with the decreased BP during the infusion of nicardipine.

ifBeta significantly decreased during the administration of nicardipine, which was thought to result from the relaxation of smooth muscle cells in the iliac-femoral artery due to the infusion of nicardipine. ifBeta exhibited a significant positive correlation with SBP, DBP, and TPR and a significant negative correlation with CO. In other words, nicardipine-induced dilation of the muscular artery decreased TPR, which led to the decrease in BP and the increase in CO. These findings suggest that ifBeta reflects part of the resistance of the muscular artery in the systemic circulation.

However, aBeta increased during the decrease in BP induced by the administration of nicardipine. aBeta negatively correlated with SBP, MAP, DBP, and TPR but did not correlate with CO. The response of the elastic arteries to nicardipine is completely opposite to that of the muscular arteries. This indicates that elastic arteries stiffen, contrasting the dilation of the peripheral arteries and decrease in BP, which is a very interesting and unexpected phenomenon. Why don't both aBeta and ifBeta change in the same direction among the arterial tree by the infusion of nicardipine which lowers BP by dilating the peripheral muscular arteries and arterioles? Similar contradictory responses of aBeta and ifBeta were also observed during the decrease in BP induced by the infusion of phentolamine<sup>13)</sup>. There exists a certain mechanism that the decrease in BP induced by the dilation of the muscular arteries might enhance the contraction of the smooth muscle cells in the elastic artery; however, such a mechanism should be elucidated in the future. This phenomenon might be one of the cross talks between the aorta and muscular arteries to maintain systemic hemodynamics, for example, to keep the blood supply to the brain when BP decreases.

aifBeta did not change significantly in response to the decreased BP induced by the infusion of nicardipine and did not correlate with SBP, CO, or TPR. aifBeta

almost corresponds to the CAVI as aifBeta reflects the stiffness from the origin of the aorta to the distal end of the femoral artery. aifBeta seems to function as a pressure-independent index of arterial stiffness at a glance.

Chiba et al.<sup>27)</sup> reported that the CAVI determined by the heart-ankle PWV (haPWV) in rabbits significantly increased after the continuous administration of nicardipine (10 µg/kg) for 10 min, which was fundamentally consistent with our results. However, there are some differences in the anesthetic regimen, dose and administration time, and BP level before the administration. They suggested that the increase in the CAVI was associated with the baroreflex-mediated increase in sympathetic activity in response to the decrease in BP induced by the infusion of nicardipine. Katsuda et al.<sup>13)</sup> previously demonstrated that aifBeta showed a slight but significant increase in response to the decrease in BP induced by the infusion of phentolamine, which is a nonselective  $\alpha$ -adrenergic blocker. This indicates that sympathetic activation mainly through the baroreflex is not associated with the increased aifBeta in our study.

In humans, Sasaki et al.<sup>28)</sup> demonstrated that efonidipine, an L-type and T-type calcium channel blocker, significantly decreased the CAVI concomitant with the decrease in BP in patients with type 2 diabetes mellitus accompanied by hypertension and nephropathy. This is incompatible with the change in aifBeta in rabbits. aifBeta corresponds to the stiffness of the overall aorta and iliac-femoral arteries, which almost corresponds to the CAVI. One reason of the inconsistency could be the difference in the proportion of the elastic and muscular arteries between the rabbits and humans as well as the rate of change in aBeta and ifBeta. aBeta increased by 17.5% from the control value, whereas ifBeta decreased by 41.0% from the control 2 min after the onset of administration. We estimated aifBeta by considering the

percentage of the length of the two arteries and that of the increase in aBeta and decrease in ifBeta. The lengths of the aorta and iliac-femoral arteries were  $261.4 \pm 9.8$  mm and  $80.5 \pm 8.3$  mm (mean  $\pm$  SD), respectively. In the present study, the elastic and muscular arteries accounted for 76.5% and 23.5% of the studied length, respectively. The estimated aifBeta on a simple calculation ( $[0.175 \times 0.765 \times 100 - 0.410 \times 0.235 \times 100] + 100$ ) was 103.7% of the control value, although the estimated value was smaller than the actual aifBeta (106.7% of the control value) 2 min after administration.

The regulatory mechanisms of the vascular tone may be different between humans and rabbits; the former is two-legged, whereas the latter is four-legged. Pathological alterations in the arteries and heart could also affect the CAVI. Kirigaya et al.<sup>29)</sup> demonstrated that CAVI was an independent long-term predictor of major adverse cardiovascular events in patients with acute coronary syndrome. Niwa et al.<sup>30)</sup> showed the relationship of CAVI with microangiopathy in patients with type 2 diabetes mellitus. Sugiura et al.<sup>31)</sup> also reported the association of obesity-related indices and metabolic syndrome with subclinical atherosclerosis in middle-aged Japanese workers. In clinical setting, the comprehensive evaluation of CAVI is required.

Yamamoto et al.<sup>32)</sup> demonstrated that the sublingual administration of nitroglycerine to healthy subjects led to the significant decrease in arterial stiffness in the muscular arteries compared with the elastic arteries. This was more prominent in patients with atherosclerosis. Their results did not coincide with our findings. Such a discrepancy may be partly due to the difference in species and also the decrease in BP.

In the future, it might be meaningful to study separately the responses to

vasoactive agents in the elastic and muscular arteries in humans.

### **Limitations**

The CAVI employed in the clinical examination includes the stiffness of the elastic and muscular arteries. The present data are not obtained from humans to whom nicardipine was administered orally but from rabbits to which nicardipine was administered intravenously in an acute experiment. It is important to elucidate the effect of the long-term administration of nicardipine to patients with cardiovascular disease on the change in stiffness in the elastic and muscular arteries in the future.

### **Conclusions**

We observed a contradictory response between the elastic and muscular arteries to the decrease in BP induced by nicardipine infusion. The increased stiffness of the elastic artery in response to the decrease in BP is considered to be caused by the contraction of the aortic smooth muscles. Unknown contractile mechanisms may exist other than the sympathetic nervous system and the inhibition of  $\text{Ca}^{2+}$  influx. The mechanism should be elucidated in the future.

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### **Conflict of Interest**

The authors have no conflict of interest concerning the present study.

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## Figure legends

Fig. 1 Schematic arrangement of the experimental setup

Fig. 2 Time-dependent changes in SBP and DBP at the oA, dA, and fA (A); CO and HR (B); TPR and MAP at the oA (C); Beta (D); and PWV (E) during the administration of nicardipine at a dose of 50 µg/kg for 2 min in rabbits

SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; HR, heart rate; TPR, total peripheral vascular resistance; MAP, mean arterial pressure; aBeta, aortic Beta; ifBeta, iliac-femoral Beta; aifBeta, overall aorta and iliac-femoral Beta; PWV, pulse wave velocity; aPWV, aortic PWV; ifPWV, iliac-femoral PWV; aifPWV, overall aorta and iliac-femoral PWV.

Fig. 3 Correlation between Beta and SBP (A), PWV and SBP (B), Beta and MAP (C), PWV and MAP (D), Beta and DBP (E), and PWV and DBP (F) during the administration of nicardipine

See the legend of Fig. 2.

aBeta significantly negatively correlated with SBP, MAP, and DBP, whereas ifBeta significantly positively correlated with SBP, MAP, and DBP. aifBeta did not correlate with SBP. aPWV, ifPWV, and aifPWV demonstrated a significant positive correlation with SBP, MAP, and DBP.

Fig. 4 Correlation between Beta and CO (A), PWV and CO (B), Beta and TPR (C), and PWV and TPR (D) during the administration of nicardipine

See the legend of Fig. 2.

aBeta and aifBeta did not correlate with CO, whereas ifBeta correlated negatively with CO. aBeta and ifBeta demonstrated significant negative and positive correlations with TPR, respectively. aPWV, ifPWV, and aifPWV exhibited significant negative and positive correlations with CO and TPR, respectively.

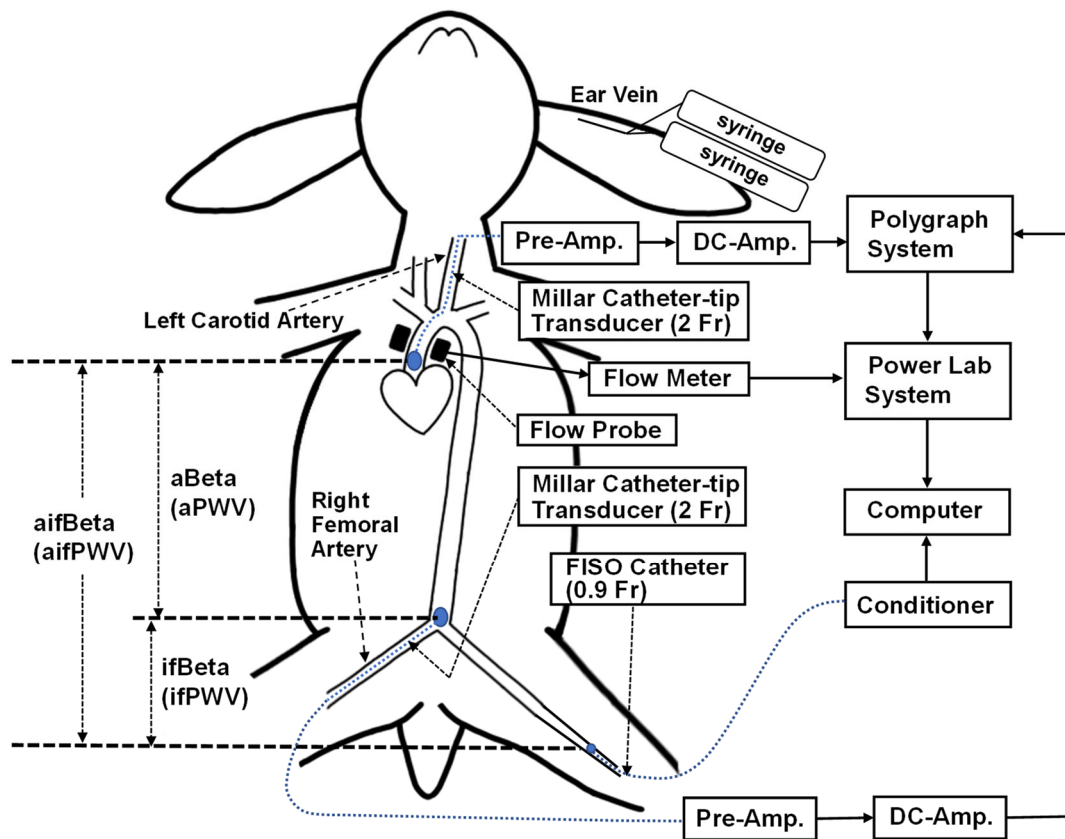


Fig.1



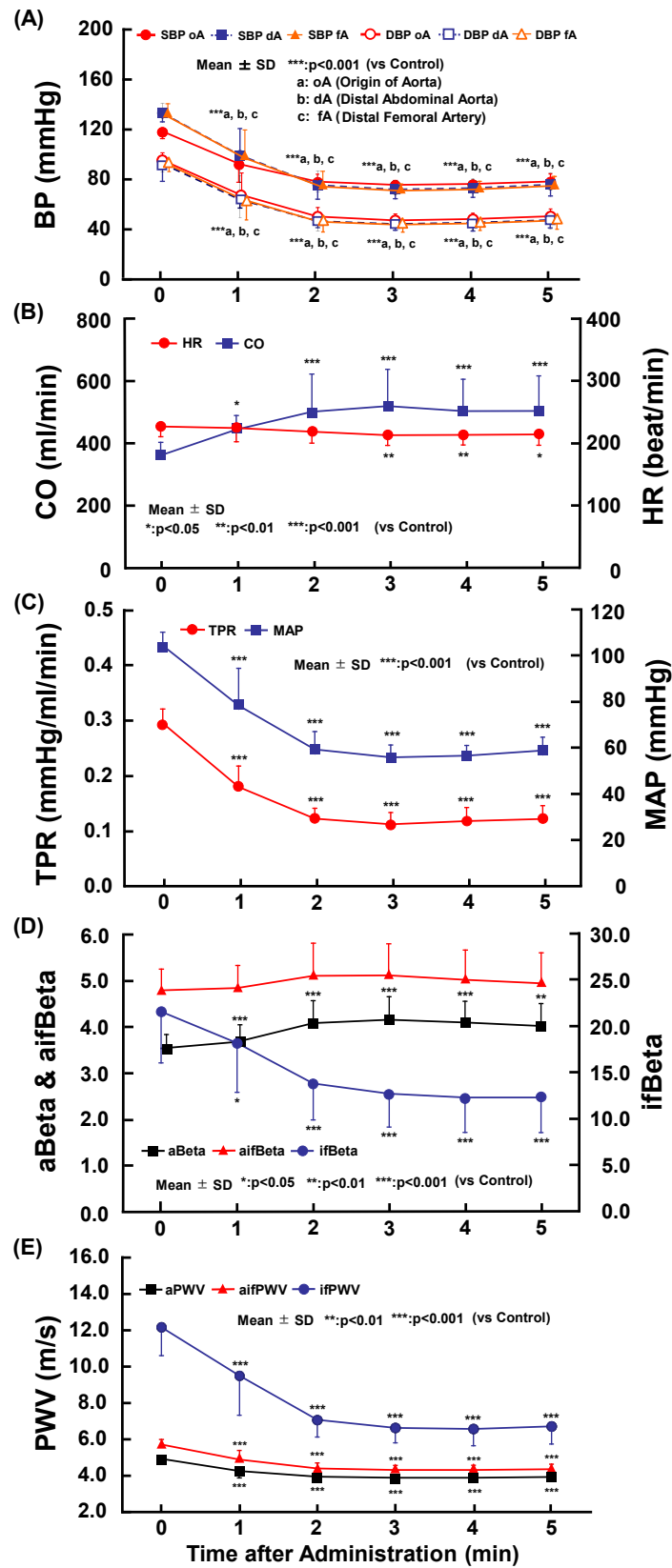


Fig. 2

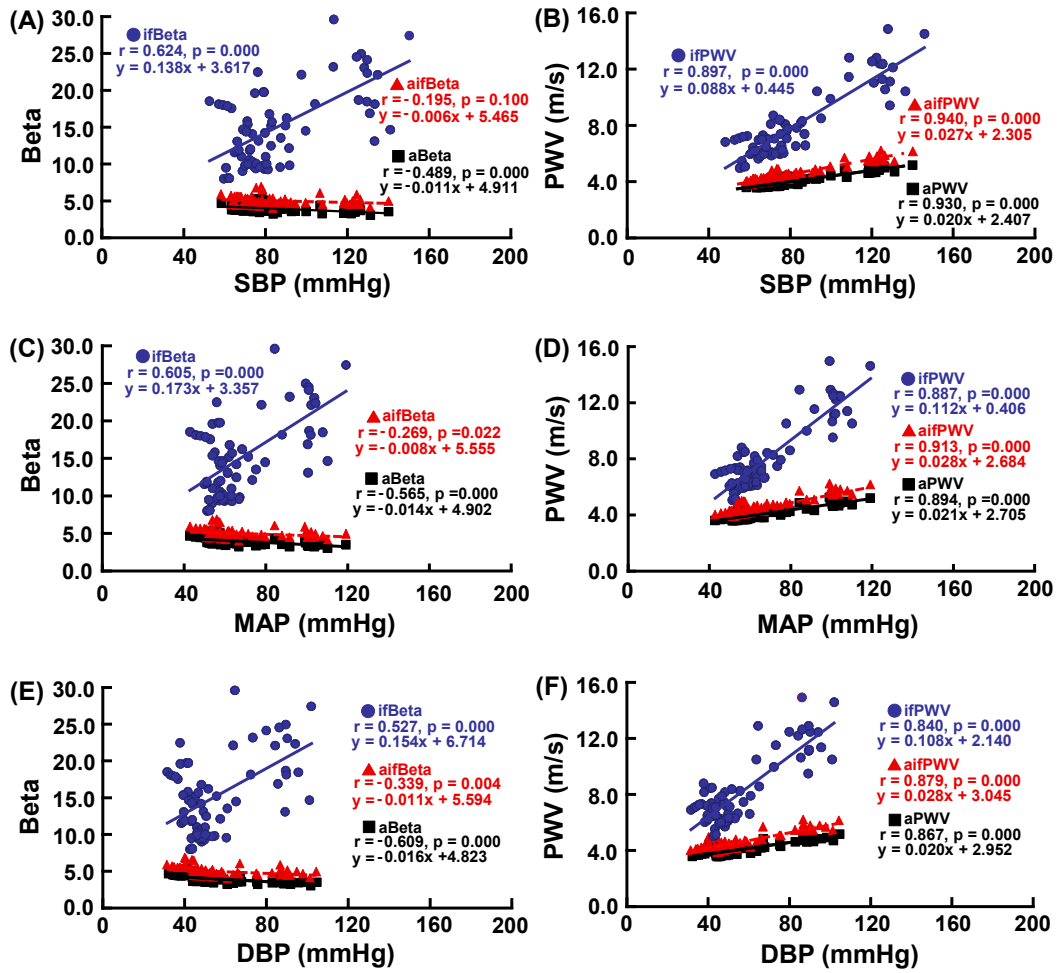


Fig. 3

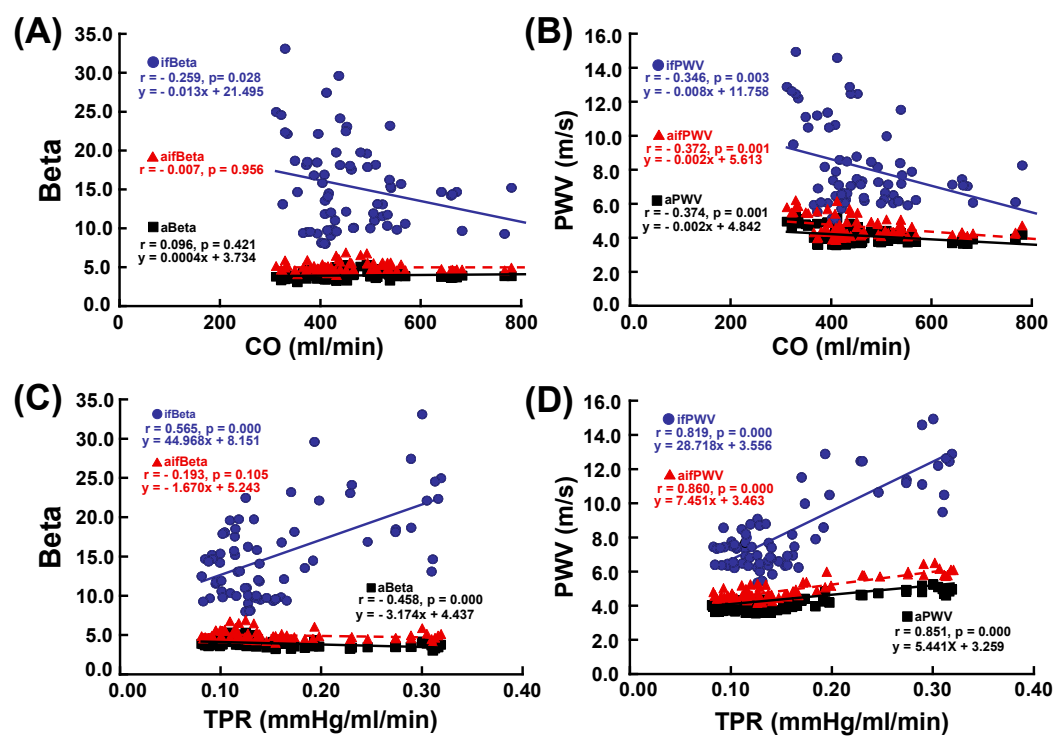


Fig. 4