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ORIGINAL ARTICLE

# The preventive effects of apolipoprotein mimetic D-4F from vibration injury—experiment in rats

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**Abstract** Hand-arm vibration syndrome (HAVS) is a debilitating sequela of neurological and vascular injuries caused by prolonged occupational exposure to hand-transmitted vibration. Our previous study demonstrated that short-term exposure to vibration can induce vasoconstriction and endothelial cell damage in the ventral artery of the rat's tail. The present study investigated whether pretreatment with D-4F, an apolipoprotein A-1 mimetic with known anti-oxidant and vasodilatory properties, prevents vibration-induced vasoconstriction, endothelial cell injury, and protein nitration. Rats were injected intraperitoneally with 3 mg/kg D-4F at 1 h before vibration of the tails for 4 h/day at 60 Hz, 49 m/s$^2$ r.m.s. acceleration for either 1 or 3 days. Vibration-induced endothelial cell damage was examined by light microscopy and nitrotyrosine immunoreactivity (a marker for free radical production). One and 3-day vibration produced vasoconstriction and increased nitrotyrosine. Preemptive treatment with D-4F prevented these negative changes. These findings suggest that D-4F may be useful in the prevention of HAVS.

**Keywords** Occupational Raynaud's · Vasoconstriction · Hand arm vibration syndrome · HAVS · Vibration injury · Endothelial cell injury · D-4F · Apolipoprotein mimetic

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## Introduction

Since the early 1900s, vibration-induced damage to the hands has been repeatedly documented in many professions requiring prolonged use of hand-held vibrating tools [13]. In the United States alone, an estimated 8–10 million workers are exposed daily to potentially harmful vibration from powered tools [23]. The symptoms associated with vibration-induced damage, called the hand-arm vibration syndrome (HAVS), include numbness and tingling of the fingers, episodic blanching of the fingers (white finger syndrome), and pain. As symptoms worsen, reductions in grip strength and finger dexterity become evident. In serious cases, vasculopathy and neuropathy can occur and lead to tissue loss of the fingertip. Unfortunately, the underlying cellular pathophysiological mechanisms leading to persistent disease remain unclear.

It is estimated that 40–90% of workers who repeatedly use vibrating tools will develop symptoms of HAVS [3]. In 1985, HAVS became a prescribed disease in the United Kingdom. Since then, it has become the most commonly prescribed disease in the United Kingdom [6]. Factors implicated in this syndrome are the intensity of acceleration, dominant frequencies (hertz) produced by the tool, and the cumulative daily exposure [21]. Current preventative measures include specific tool designs that dampen vibra-

tion and governmental regulatory directives, such as SI 2005/1093 that limit cumulative daily exposure.

Our previous study demonstrated that short-term vibration exposure was sufficient to induce vasoconstriction and endothelial cell damage in the ventral artery of the rat's tail. Exposure to vibration for 5 min demonstrated significant vasoconstriction with diminished blood flow through the affected artery. Exposure to a single session of vibration for 4 h resulted in detectable endothelial cell damage. Daily 4-h exposure to vibration led to extensive endothelial cell death by 9 days [7]. Currently, nifedipine and other calcium channel blockers are given to reduce vascular spasm intensity, and frequency; however, no pharmacologic means of prevention exist [3,8]. D-4F is a synthetic peptide that resembles human apolipoprotein A-1 molecule (apo A-1), a major constituent of high-density lipoprotein (HDL). D-4F has been shown to reduce free radical production and improve vasodilatory activity by restoration of nitric oxide and superoxide balance and lowering cytotoxic peroxynitrite production [18,19]. Given the current thinking that vibration-induced endothelial cell injury is associated with vasoconstriction resulting from the imbalance between nitric oxide and superoxide, we postulate that D-4F will minimize vibration-induced vasoconstriction and associated endothelial cell injury. The present study investigates the effects of D-4F on vibration-induced endothelial cell injury using the rat-tail model.

## Materials and Methods

Male adult Sprague–Dawley rats weighing between 250 and 300 g were acclimated for 7 days after arrival, then randomly assigned to nine groups ($n$=8 per group): group 1: normal control without any treatment; group 2: 1-day sham vibration (the rats were secured on the platform without actual vibration for 1 day); group 3: 1-day sham vibration with D-4F injection; group 4: 1-day vibration; group 5: 1-day vibration with D-4F injection; group 6: 3-day sham vibration; group 7: 3-day sham vibration with daily D-4F injection; group 8: 3-day vibration; group 9: 3-day vibration with daily D-4F injection (Table 1).

The rats were housed in the AAALAC accredited Biomedical Resource Center at the Medical College of Wisconsin. Rats were transported during the morning light cycle to the research laboratory, vibrated or sham-treated for 4 h. Normal control rats remained in standard plastic cages with bedding and were neither restrained nor vibrated. Sham vibration rats were restrained but not vibrated. The protocol was approved by the Institutional Animal Care and Use Committee at the Medical College of Wisconsin.

Sham vibration rats were placed in the restraint tubes for 4 h with ventilated caps surrounding their heads, as previously described [9]. Rats were acclimated for 7 days to daily handling and restraint in the tubes before beginning treatment. The rats voluntarily entered the restraint tubes and typically rested during vibration. Each restraint tube was secured to a non-vibrating platform, separated from the vibrating platform by a 1-cm gap. The tails were taped to a metal platform that was vibrated for the vibration groups and not vibrated for the sham controls. Vibration and sham periods were begun at 8 a.m. To control for environmental parameters, sham and vibrated groups were conducted concurrently in the same room.

Vibration treatment was 4 h per day continuously at 60 Hz, 49 $m/s^2$ r.m.s. acceleration for either 1 or 3 consecutive days. The vibration platform was vertically accelerated by a Brüel and Kjær motor (type 4809) powered by a type 2706 amplifier (Brüel and Kjær, Norcross, GA). Vibration parameters were set and rechecked with a Brüel and Kjær Integrating Vibration Meter. Frequency was controlled by a sine wave generator (GW Instek America Corporation, Chino, CA).

D-4F, the apo A-1 mimetic peptide, was synthesized by the Protein and Nucleic Acid Shared Facility of the Medical College of Wisconsin and the Blood Center of Wisconsin. The peptide was reconstituted in normal sterile saline. All rats received intraperitoneal injections 1 h prior to the initiation of the vibration experiment protocol. The rats in groups 3, 5, 7, and 9 received intraperitoneal injection of D-4F (3 mg/kg). All other rats received intraperitoneal injection of sterile saline.

After completing 4-h vibration, the rats remained in the restraint tubes for 1 h to allow expression of NFATc3 transcription factor, which will be examined in a future study [7]. The rats were then anesthetized with 35 mg/kg of intraperitoneal sodium pentobarbital (Phoenix Pharmaceutical, Inc. St. Joseph, MO). The tail skin was removed, and the caudal segments C5–C8 were isolated by cutting transversely through the intervertebral joints with a sharp scalpel blade. The segments were immersion-fixed solutions overnight at room temperature. Segments C5, C6 were treated with 10% paraformaldehyde in 0.1 M phosphate buffered at pH 7.4 for light microscopy, segments C7, C8 were treated with 0.25% glutaraldehyde. The next day, the fixed segments were washed three times in 0.1 M phosphate buffer (pH 7.4) and refrigerated in fresh buffer. The arteries in segments C5 and C6 were dissected under the microscope for paraffin embedding. The tissues were progressively dehydrated in 30%, 50%, and 70% ethanol solutions (10 min in each solution) before routine embedding in paraffin wax. Blocks were stored at 4°C until sectioned. Arteries from the C7 and C8 segments were dissected under the microscope and postfixed with 1.3% osmium tetroxide, processed, and embedded in epoxy resin as described previously [11].

**Table 1** Summary

| Group | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Description | Control | 1-day sham | 1-day sham+ D-4F | 1-day vibration | 1-day vibration+ D-4F | 3-day sham | 3-day sham+ D-4F | 3-day vibration | 3-day vibration+ D-4F |
| Time on platform (days) | 0 | 1 | 1 | 1 | 1 | 3 | 3 | 3 | 3 |
| Vibration duration (days) | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 3 | 3 |
| D-4F injection (times) | 0 | 0 | 1 | 0 | 1 | 0 | 3 | 0 | 3 |
| Ratio of vasoconstriction[a] | 0.524± 0.144 | 0.455± 0.102 | 0.468± 0.086 | 0.324± 0.079 | 0.481± 0.086 | 0.454± 0.057 | 0.443± 0.089 | 0.309± 0.03 | 0.422± 0.039 |

[a] The degree of vasoconstriction was defined as the lumen circumference divided by the length of the internal elastic membrane times 100 [8]

Paraffin sections were cut at 6 μm for immunohistochemistry. The sections were dewaxed with two 100% xylene rinses (5 min for each rinse) followed by progressively rehydrating in decreasing ethanols to phosphate-buffered saline. Sections were held in phosphate-buffered saline for 30 min before indirect immunoperoxidase staining for nitrated tyrosines by incubating with rabbit anti-nitrotyrosine (1:250, Upstate Biotechnology, Lake Placid, NY) followed by goat anti-rabbit IgG [5]. Superoxide combines with nitric oxide (NO) to generate peroxynitrite, which nitrates tyrosine residues of proteins to form nitrotyrosine. Peroxidase staining was developed with a Vector ABC kit and Vector blue and counterstained with nuclear fast red (Vector Laboratories, Burlingame, CA). Omission of the primary antibody controlled for nonspecific labeling of the secondary antibody. Blocking with 1.5% normal goat serum reduced nonspecific binding.

Images of immunostained cross-sections of whole arteries were captured digitally with a Zeiss AxioVision light microscope (Zeiss, Germany). To quantify immunoperoxidase staining, sections from all group arteries were incubated together and photographed digitally at the same exposure and light intensity setting and ×20 magnification. Optical density of staining was analyzed using MegVue 5.0r7 software (Universal imaging Corporation, Downingtown, PA), with four regions positioned at 3, 6, 9, and 12 o'clock sampled per artery. The values from the four regions were averaged to derive the mean optical density for the artery.

Semi-thin, epoxy cross-sections (0.5 μm) were cut, stained with toluidine blue, and digitally imaged for computer-assisted measurement of the artery lumen circumference and length of the internal elastic membrane. Version 1.28v ImageJ Software (National Institutes of Health, Bethesda, MD) was used to measure lumen circumference and determine internal elastic membrane length. The degree of vasoconstriction was defined as the lumen circumference divided by the length of the internal elastic membrane times 100 [8]. Vasoconstriction was compared using a one-way analysis of variance with Bonferroni correction and independent samples *t* test. Statistical analysis was performed using GraphPad Software (San Diego, CA). Differences were considered significant if $p<0.05$. Values are presented as means ± SEM.

## Results

### Lumen Size

As observed previously, 4 h of continuous vibration at 60 Hz delivered for 1 or more days caused reduction in the caliber of the rat-tail ventral artery [11]. The decrease in lumen size was prevented by 1- and 3-day of D-4F treatment (Fig. 1). D-4F treatment of the sham vibration groups (groups 2 and 6) produced no detectable difference in lumen size when compared with the control group (group 1). Vibration-induced cellular damage was similar to that described previously in constricted arteries; endothelial cells were severely compressed and protruding into the lumen [9].

### Nitrotyrosine Immunoperoxidase Staining

Intense immunostaining for nitrotyrosine was present in the walls of the arteries of the 1- and 3-day vibration groups (Fig. 2). Sham vibration groups (groups 2 and 6) and sham vibration with D-4F injection groups (groups 3 and 5) exhibited little or no immunostaining (Fig. 2). The 1- and 3-day vibration with D-4F groups showed significantly lighter staining than their respective vibration groups (Fig. 2). The result shows that D-4F significantly reduces the amount of vibration-induced tyrosine nitration (a marker for free radical production). Optical density quantitation of the immunoperoxidase immunostaining revealed that vibration for 1- and 3-day produced darker staining of the tunica media compared to the sham vibration groups and the vibration groups treated with D-4F (Fig. 3).

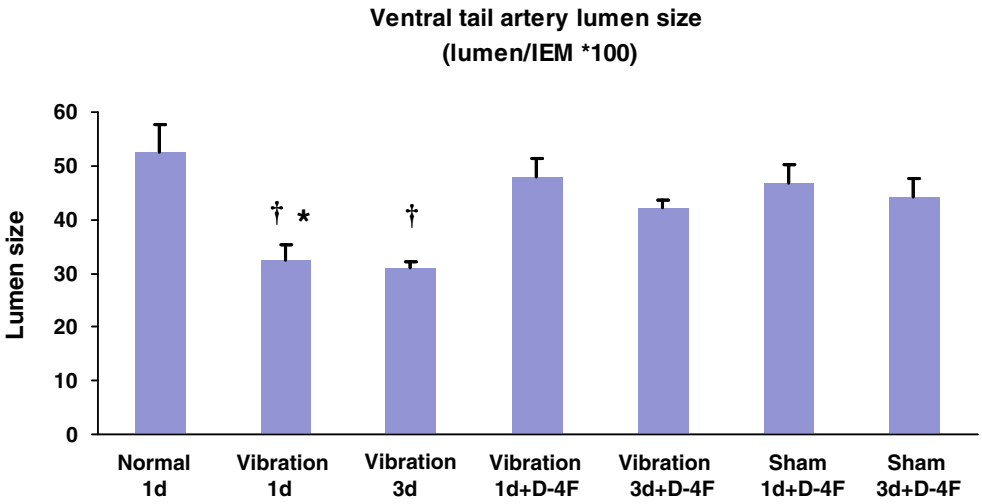


**Fig. 1** Vibration for 1 or 3 days causes reduction in lumen size compared to that of normal control arteries. Treatment with D-4F prevents vibration-induced vasoconstriction. D-4F injected sham groups are not different from control (†$p<0.01$ vibration versus control; *$p<0.05$ vibration 1-day versus vibration 1-day+D-4F)

## Discussion

As expected, rat-tail vibration for 1- and 3-day (4 h per day) produced vasoconstriction and increased nitrated proteins in the tunica media of the ventral artery [11,12]. Remarkably, D-4F treatment minimized the amount of vasoconstriction and protein nitration in the ventral artery of the rat-tail.

Current thinking on vibration-induced vasculopathy suggests that vasoconstriction is caused by central and local factors. Indirect evidence points to centrally generated sympathetic outflow triggered by afferent input from pacinian vibroreceptors activating the somatosympathetic reflex [20]. Locally, sensitivity to norepinephrine increases because of translocation of $\alpha_{2C}$ receptors to the smooth muscle cell membrane [14]. The resulting vasoconstriction reduces blood flow, creating ischemic conditions and production of superoxide anions. Superoxide combines with nitric oxide (NO) to generate peroxynitrite, which nitrates tyrosine residues of proteins. This consumption of NO reduces NO bioavailability for vasodilation. In addition, nitration of endothelial nitric oxide synthase (eNOS) inhibits eNOS activity and decreases NO synthesis [24]. To make matters worse, when exposed to free radical such as peroxynitrite, eNOS (which normally exists as a homodimer and generates NO) uncouples to monomeric form, which acts as NADPH oxidase and generates superoxide

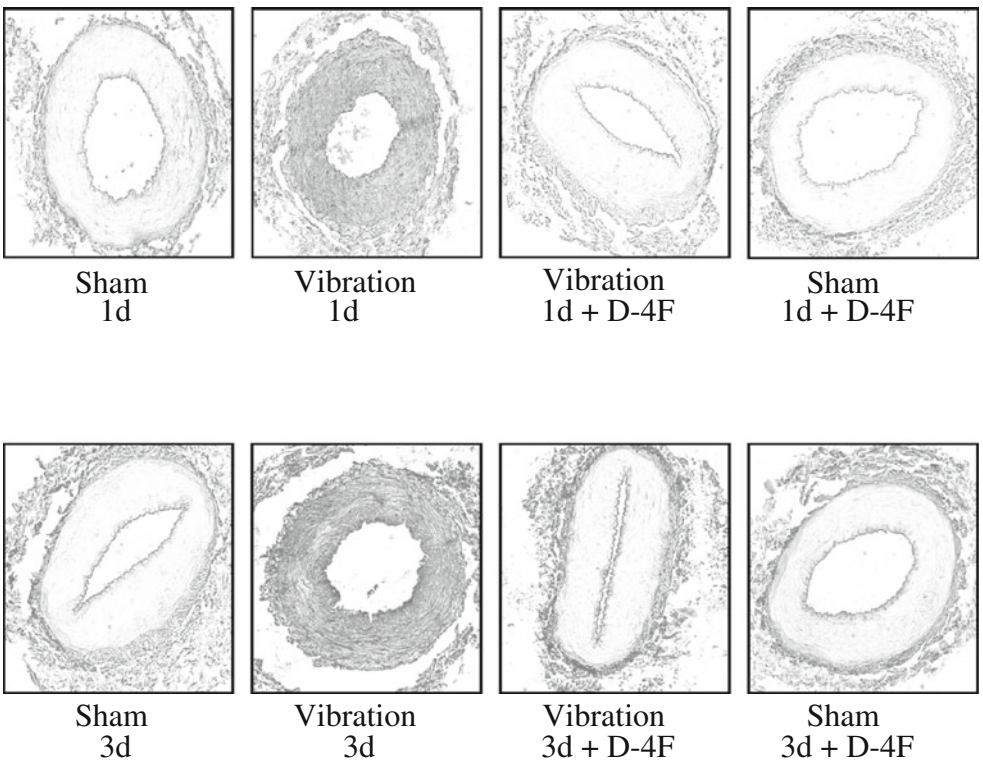


**Fig. 2** Comparison of nitrotyrosine immunoperoxidase staining of artery cross-sections

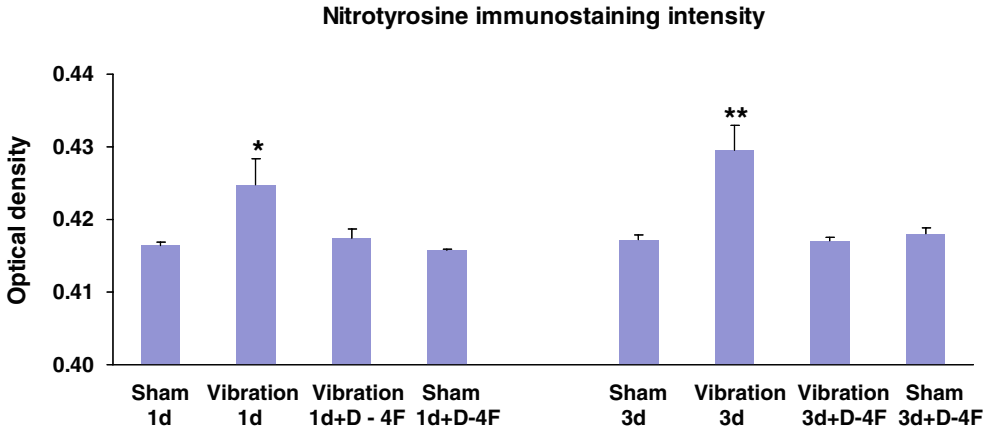


**Fig. 3** Intensity of immunoperoxidase staining of the arterial wall. Immunoreactivity for nitrotyrosine was marked elevated after 1- and 3-day vibration, compared to non-vibrated, restrained sham groups (sham 1, 3 days). D-4F treatment blocked the increase in nitrotyrosine during vibration (vibration+D-4F). No effect of D-4F was detected on non-vibrated restrained sham 1- and 3-day groups (*$p<0.05$ vibration 1-day is different from the vibration 1-day+D-4F, sham 1- and sham 1-day+D-4F groups; **$p<0.01$ vibration 3-day is different from all other 3-day groups)

rather than NO [25]. Furthermore, during vibration-induced vasoconstriction, endothelial cells are physically distorted and injured by tight pinching between folds of the internal elastic membrane [9]. These distorted endothelial cells are subjected to increased shear stress from blood flow, which triggers NADPH oxidase and xanthine oxidase to generate superoxide [10]. The increase in superoxide formation and the decrease in NO production fuel the vicious self-perpetuating cycle of vibration-induced vasoconstriction/ischemia and endothelial cell injury.

Apolipoprotein A-1 (apo A-1), the main protein component of the HDL, is a 243-amino acid protein synthesized in the intestine and liver. The ability of HDL to remove lipids (cholesterol and phospholipids) from peripheral tissues and vessel walls is mediated by apo A-1 and its interaction of lipids. Various short synthetic peptides have been made to mimic the function of apo A-1 (i.e., apo A-1 mimetic) without bearing any sequence homology to apo A-1. Specifically, several 18-amino acid peptides with variable number of phenylalanine (F) residues (2F, 3F, 4F, 5F, 6F, 7F) had been shown to enhance hydrophobicity and increased lipid binding efficacy, thus increasing the effectiveness of HDL [17]. Interesting, despite similar amino acid composition and hydrophobicity, the subtle differences in the three dimensional structure of these apo A-1 mimetic peptides have been shown to result in marked variability in their biologic actions, with 4-F showing the highest potency for anti-inflammatory action in cell culture models [17]. In addition to its role in lipid transport, apo A-1 is also crucial in the anti-inflammatory properties of HDL [2]. D-4F has also been shown to possess similar anti-inflammatory properties. D-4F binds non-oxidized lipids and sequesters fatty acid hydroperoxides and pro-inflammatory oxidized phospholipids [1].

What specific attributes of D-4F are postulated to counter vasoconstriction, cell damage, and nitration induced by vibration injury? D-4F has been shown to have significant anti-oxidant effect by improved acetylcholine-mediated eNOS-dependent vasodilation and restores a safe balance of nitric oxide and superoxide anion generation in endothelial cells [19]. With preservation of eNOS function and without superoxide excess, peroxynitrite is not generated to trigger vasoconstriction and to cause endothelial cell damage. Our study confirms the anti-oxidant effect of D-4F as it significantly reduces the amount of vibration-induced vasoconstriction as well as protein nitration in the ventral artery of the rat-tail. In addition, human and mice HDL treated with D-4F have been shown to be significantly more anti-inflammatory, as judged by the diminished monocyte chemotactic activity generated by LDL-treated human aortic endothelial cells [17]. The anti-oxidant and anti-inflammatory properties of D-4F make it a potential antidote for vibration-induced endothelial cell injury (Fig. 4) and are what motivated us to test its effects in the rat-tail model.

With regard to the effective dosing of D-4F, pharmacological studies have shown that it is effective in vivo in nanomolar concentration [22]. Earlier D-4F studies in endothelial cell culture model reported using D-4F in final concentration of 10 ug/ml (equivalent to 10 mg/kg) [19], while studies using the rat model reported using 1 mg/kg administered via intraperitoneal injection [15]. In the first published human trial, oral D-4F was administered at 30, 100, 300, or 500 mg doses to the subjects. Assuming the average weight of 75 kg for each subject, the calculated dosing concentration would be 0.4, 1.3, 4, and 6.7 mg/kg, respectively. In that study, the 4 and 6.7 mg/kg dosings

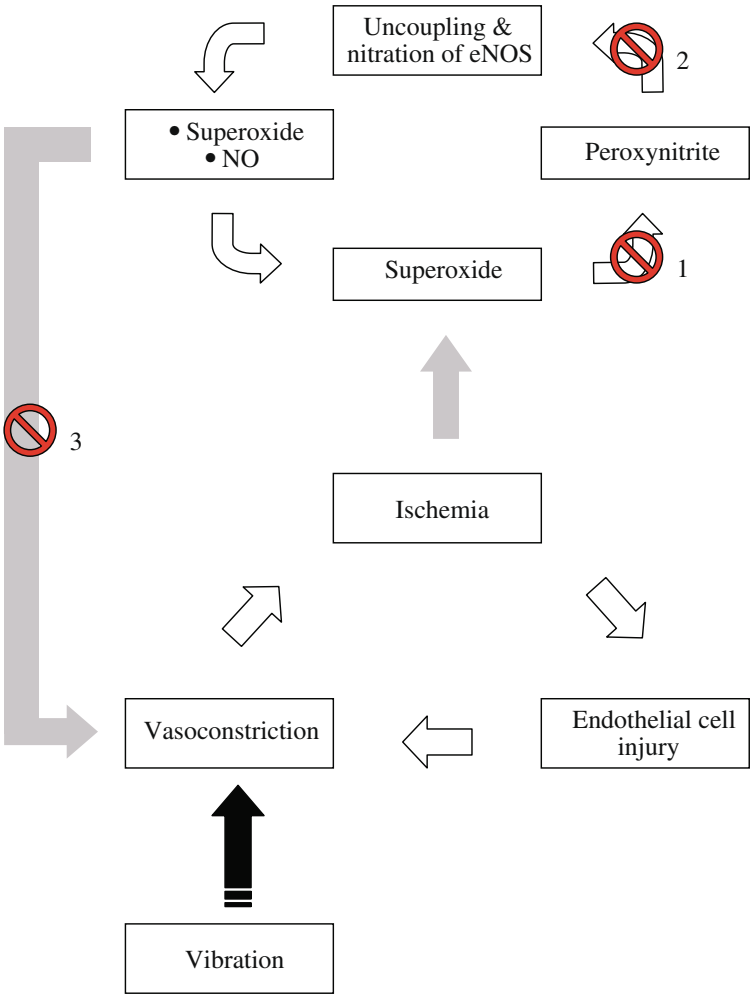


**Fig. 4** Proposed sites of action for D-4F for vibration-induced endothelial cell injury

Proposed sites of D-4F action:
1. Anti-oxidant property prevents conversion of superoxide into peroxynitrite
2. Prevents nitration and uncoupling of eNOS →restores safe balance of superoxide and NO
3. Combined effects of 1 and 2 minimize vasoconstriction and break the self-perpetuating cycle of vibration-induced vasoconstriction/ischemia and endothelial cell injury

were found to significantly improve the HDL anti-inflammatory index [4].

Unlike most other peptides that would be broken down if administered orally, D-4F can be absorbed through the gastrointestinal tract without degradation. All amino acids except glycine can exist in two forms as optical isomers (i.e., mirror images of each other), the L form or the D form. Because mammalian enzymes recognize and degrade peptides made from L-amino acids but generally spare peptides made from D-amino acids, D-4F (the D form of the 4F peptide) had been demonstrated to be bio-available upon oral administration in mice and human [4,16]. In human subjects, oral D-4F is well tolerated, rapidly absorbed, and results in a low but dose-dependent plasma concentration. To date, no significant adverse reaction in human has been reported. Minor reactions include arthralgia, diarrhea, dizziness, and headache. The frequency of adverse reaction does not appear to be dose related. The absorption rate is improved by fasting and reaches peak serum level within 4 h of oral administration [4].

Although 1 mg/kg dosing has been demonstrated to be efficacious in the rat model, the study using such dosing treated the rats with D-4F for 6 weeks [15]. In contrast, our experiment only treated the rat for up to 3 days. We arbitrarily increased the treating dose to 3 mg/kg for our short-term study, in hope that the higher dosing will maximize the demonstration of the beneficial effects of D-4F. It is our intention to investigate the effect of different D-4F dosing (e.g., 1, 2, 3, and 4 mg/kg) on vibration-induced vasoconstriction, endothelial cell damage, and protein nitration in the rat-tail model and to develop a

dose–response curve in our subsequent studies. Further studies are also needed to determine which of the manifold protective actions of D-4F are actively protecting arteries from vibration injury in the rat-tail model. The knowledge gained from these studies may prove to be useful in the prevention of HAVS.

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**Conflict of Interest** The authors declare that they have no conflict of interest.

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