Improved Animal Model for Vibration Injury Study

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Summary
Hand-Arm Vibration Syndrome is a debilitating condition that affects millions of power-tool users in the U.S. Research into its etiology has been hampered by deficiencies in animal models used for vibration studies. Our objective was to design an animal vibration injury model that: 1) vibrates only the studied limb, not the body; and 2) avoids anaesthesia, thus allowing purer focus on physiological effects of vibration while reducing pain and distress for the animals, thereby enhancing their well-being. We compared advantages and disadvantages of several models, studying body temperature, body weight, tissue perfusion, vascular pathohistology, and general animal condition. Our model uses an apparatus that limits vibration to one body part and a specially designed cage that minimizes animal stress and suffering, eliminating the need for anaesthesia. It is ideal for the study of vibration injury, providing tissue damaged purely by vibration that can be used for pathohistology and biochemical study.

Introduction
The etiology of Hand-Arm Vibration Syndrome (HAVS) at the cellular and molecular level is still unclear. Investigators have studied this topic for many years, frequently using the animal model involving vibration on rat's leg during whole animal anaesthesia (*Yan et al., 2005; Matloub et al., 2005; Lundborg et al., 1987; Lundborg et al., 1990*). However, an important question has been raised: Is this model comparable with human HAVS?

For almost a century, workers who operate vibration tools on the job have reported complaints resembling the signs and symptoms of a primary Raynaud's disease. The major complaints were episodic numbness and tingling of the fingers, episodic blanching of the fingers, the so-called "Vibration-induced White Finger" (VWF) or HAVS (*Olsen et al., 1988; Sakakibara et al., 1988; Bovenzi, 1998; Noël, 2000; Palmer et al., 2000; Lindsell and Griffin, 1999; Kennedy et al., 1999; Bovenzi et al., 1997; NIOSH, 1989; Ryan et al., 2005; Ziegler et al., 2005; Carlsson et al., 2003; Cherniack et al., 2004; Hiratai et al, 2004; Hubbard et al., 2004; Kakosy et al., 2003; Morse et al., 2003; Mason et al. 2003; Cederlund et al., 2003; Lundborg et al., 2002; Adamo et al., 2002; Bylund et al., 2002; Weir and Lander, 2005*). In 1918, Alice Hamilton, an early worker in this field, investigated this syndrome, prolonged exposure to vibration, and reported debilitating vascular, neurological, and musculoskeletal problems. An estimated 8-10 million workers use vibrating tools in the United States (*Wasserman, 1987*). In workers who have used vibration tools, the prevalence of HAVS ranges from 6% to 100%, with an average of about 50% (*Harada et al., 1999*). The patients experience reduction in grip strength and finger dexterity and eventual neuropathy. They may develop carpal tunnel syndrome, cubital tunnel syndrome, or other nerve entrapment syndromes. HAVS is

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a chronic disorder, with a latency period of a few months to several years. The early stages of HAVS are usually reversible if future exposure to vibration is reduced or eliminated, but otherwise the condition will progress. Treatment is usually ineffectual in the advanced stages of HAVS, and the disorder can progress to loss of effective hand function and in very serious cases, necrosis of the fingers (*Bovenzi et al., 1999; Bovenzi et al., 2000a; Färkkila et al., 1988; Hagberg et al., 1991; Sakakibara et al., 1988; Taylor, 1986; Bovenzi et al., 1991; Bovenzi et al., 1994; Cherniack et al., 2000; Takeuchi et al., 1988; Jack, 2005; Meloni et al., 2004; Koton, 2002; Issever et al., 2003; Lundborg et al., 2002; Adamo et al., 2002; Falkiner, 2003*).

Prevention and treatment of vibration injury present a great challenge for hand surgeons and for occupational medicine physicians. Because the pathological process of vibration injury is poorly understood, it is very important to study this process (*Ho and Yu, 1989; Bovenzi et al., 2000b; Matsumoto, 1987; Kurozawa and Nasu, 2000; Dahlin et al., 1992; Hoque et al., 1996; Ziegler et al., 2005; Hubbard et al., 2004; Herrick et al. 2005; White et al., 2004; Falkiner, 2003*). Many universities and research institutes use animal models. In studies on this topic, for many years the animal models were very similar, using vibration on rat's leg under anaesthesia. This practice, however, evoked an important question: Is this model comparable to human HAVS? The answer is no, because human HAVS is developed in the unanesthetised state through the use of tools by hand. In our institution we have studied vibration injury since 1988, developing and refining our animal model in the course of this work in an attempt to minimize animal stress and maximize quality of research data. In this paper, three different animal models are compared and analysed.

Materials and Methods

Over twenty years we have utilized three different models, refining our apparatus and comparing the advantages and disadvantages of each model for particular aspects of vibration injury study. Animal care complied with the guidelines of our own Institutional Animal Care and Use Committee (IACUC) and follows the *Guide for the Care and Use of Laboratory Animals*.

Model I – Rat leg vibration with whole animal anaesthesia

This model has been widely used around the world (*Lundborg 1987, 1990; Matloub et al, 2005; Yan et al., 2005*). Our first study (1988-1995) explored vibration exposure and its effect on axoplasmic transport in the peripheral nerve system. Sprague-Dawley male rats weighing 180 to 200 grams were used in our study (Yan et al., 2005). All animals were anesthetized by intraperitoneal injection of pentobarbital 3.5 μg/100 g of weight. The rats were then placed on a vibration apparatus consisting of two platforms: a vibrating platform on which the hind limbs of the rat were secured with Velcro straps, and a stationary platform on which the rest of the body was secured. Each foot of the stationary platform was fitted with an individual steel spring base, which prevented transfer of vibration (Fig. 1). The vibrating platform was separated from the stationary platform by a 1.5-cm gap. A 120-volt motor obtained from a massager machine, (Oster, 2 intensity Swedish hand massager, PNER 24-K, Division of Sunbeam Corp., Milwaukee, WI) was firmly bolted to the underside of

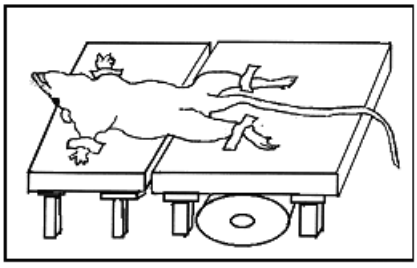

Figure 1. Model for vibration of rat hind limbs. Rat rests on two separate platforms. The rat's upper body and trunk rest on a platform that is separated from the vibration platform; hind limbs are on the vibration platform.

the vibrating platform. The vibrating platform was then suspended by springs from four steel rods. A piezoelectric accelerometer (Bruel & Kjeer Model Integrating Vibration meter, Type 2516) was affixed to the vibrating platform by a magnet to constantly monitor the vibration parameters. A cooling fan was placed in the vibration chamber to cool the motor, thus maintaining the temperature of the vibrating platform and excluding any thermal component of the vibration exposure.

Model II – Rat tail vibration with whole animal anaesthesia

In following years we explored physiological changes to peripheral nerves and vasculature at the cellular and molecular levels (*Curry et al., 2005; Yan et al., 2005*). In this study the animal groups were the same as those in the earlier study, but rat tail was used for vibration instead of the hind leg. The anaesthesia method was also changed. Rats were deeply anesthetized with a Ketamine 72 mg/kg Xylazine 12 mg/kg, and acepromazine 0.04 mg/kg mixture injected into the quadriceps muscle. The vibration platform set-up was the same as in our earlier model: A vibrating motor was firmly secured to the end of the vibrating platform; the vibrating platform was set up to be separate from the other, stationary platform so that only the rat's tail was vibrated, while the rest of the body was not.

Model III – Rat tail vibration of awake rat

In our current research, we continue to study cellular and molecular change in vessels and peripheral nerve in an attempt to find ways to prevent and treat vibration syndrome. A total of 80 animals have been studied.

In Model III there were two major modifications in the animal model. 1) The rats were not subjected to anaesthesia. 2) The rats were housed in vivarium plastic box cages in an animal holding room at 25°C in 12/12-hour dark/light cycles. After the animals were moved from the Animal Resource Center to the Animal Research Laboratory and given a 20-minute calm time for rest, every animal instinctively sought out the small cage. In the vibration group, the rats were placed individually in small cages (*Curry et al., 2002*). Their tails were held on the vibrating platform as described below. Sham control rats were processed concurrently with vibrated animals. The sham controls were handled analogously, with their tails held on the same platform, but without vibration. The small cage was manufactured in-house from 2-inch internal diameter PVC (polyvinyl chloride) pipe. This pipe enclosed the body and a wire mesh cage surrounded the head (See Fig. 2A.) Drilled holes permitted air exchange and gravity-fed exiting of urine and faeces. The small cage was bolted to a non-vibrating platform, which was separated from the vibration platform by a 1-cm gap. Custom form-fitted plastic splint molds (Polyform, Smith-Nephew) confined the tails to the linear vibrated platform. During vibration, the splints were affixed to the vibrating platform with Velcro® strips. Vibration consisted of linear vertical oscillations of 60 Hz and 5G acceleration (49 m/s^2) for four or five hours a day vibration and for either 1, 3, 5, 9, 10, or 14 days. During a standard four-hour session, acceleration drifted less than 2 m/s^2 and frequency shift-

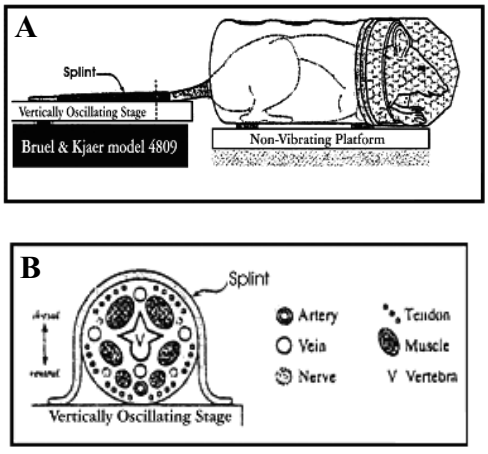

Figure 2. (A) Rat tail vibration model: The rat is in the restraint tube on the non-vibrating platform, and the tail is placed on a separate vibration platform. (B) Cross section of typical rat tail.

ed less than 1Hz. Acceleration of the non-vibrating platform varied less than 1 m/s^2. Accelerometer placement on the tail measured 5G acceleration, indicating tight coupling to the accelerating platform. The electromagnetic vibration accelerator, a Brüel and Kjaer (B&K) PM Vibration Exciter Type 4809, was driven by a Simpson 420 Function Generator in sine wave form. The signal was augmented by B&K Power Amplifier Type 2706. Frequency and acceleration were checked daily with an H 1201B oscilloscope and a B&K accelerometer mounted on a B&K Integrated Vibration Meter, Type 2513.

In each animal model, eight animals were chosen randomly for monitoring of body temperature and body weight changes or for observation of the animals' condition with different treatments. Tissue perfusion in rat tail arteries was measured using a BLF 21 Laser Doppler apparatus (Transonic System, Inc.) coupled to a Gould Brush 220 chart recorder. Tissue perfusion studies were done in all models. Body temperature was measured using microelectronic thermometers (Electro-therm Digital Thermometer SH66A, USA) with a small probe inserted into the rat's rectum, which continued to measure the rat's temperature for six hours.

The tail arterial sections were compared in different treatments: anaesthesia without vibration, anaesthesia with vibration, vibration without anaesthesia, and normal without any treatment.

Results

This study compared characteristics, advantages, and disadvantages of different animal models for vibration injury.

Avoidance of stress and body vibration injury

In Model I, upon awakening from anaesthesia, animals exhibited signs of stress, biting the cage and even biting handlers. One fourth of the animals had hematuria, porphyrin secretion around the eyes (chromodacryorrhea), unkempt coat indicative of poor self-grooming, and a generally sick appearance, possibly due to transfer of vibration to the body. By contrast, rats in Model III accommodated to the small restraint tubes with calm and displayed only a brief startle response of the head when the vibration platform was activated (Fig. 2). After vibration, the rats immediately walked around and maintained normal intake of food and water. In Model I, each animal needed, on average, one additional intraperitoneal injection to maintain anaesthesia. These repeated injections increase the risk and occurrence of injury to internal organs.

Body temperature in different conditions

Four conditions were studied: normal, anaesthesia, anaesthesia with vibration, and vibration without anaesthesia. Temperature data for these four conditions is given in Table 1. After one hour of anaesthesia, in anesthetized rats without vibration the body temperature decreased an average of 3.8°C, from a mean of 37.3°C to 33.5°C. This lower temperature persisted for five hours. These results compare to normal rats without any treatment (mean 37.1°C to 37.0°C) after five hours. In the anaesthesia with vibration group, the body temperature went from a mean of 37.3°C to 33.6°C, an average decrease of 3.7°C. These results are almost the same as in the anaesthesia without vibration group. In Model

Table 1. Rat's body temperature change. Temperatures expressed in °C; n = 10

	Normal	**Anesthesia**	**Anesthesia & Vibration**	**Vibration**
0 hours	37.1 ± 0.7	37.3 ± 0.5	37.3 ± 0.5	37.0 ± 0.5
1 hour	37 ± 0.6	33.5 ± 0.9	33.4 ± 0.8	37.1 ± 0.4
5 hours	37 ± 0.4	33.1 ± 0.6	33.6 ± 1.2	37.2± 0.5
Change after 5 hours	-0.1	-4.2	-3.7	+0.2

III, in rats who received vibration without any anaesthesia, the body temperature remained constant, around the normal body temperature of 37° C.

Body weight change associated with vibration in different models (Table 2)

Ten rats in different treatment groups (normal, anaesthesia, anaesthesia with vibration, and vibration without anaesthesia) were randomly selected for this study. In normal rats without any treatment, after nine days, the body weight increased 53.5 g. The percentage increase was 26.6%, a normal growth rate. In the anaesthesia group after nine days, the body weight increased only 6.6 g. (a percentage increase of 3%). In the vibration with anaesthesia group, the body weight increased 21.7 g, (a 9.8% increase). In the vibration without anaesthesia group, the body weight increased 31.8 g (an increase of 14.4%), (Table 2). When the body weight of the anaesthesia group is compared with that of the normal group, the difference is statistically significant ($p<0.001$). In a comparison of results in the vibration without anaesthesia group with those in the vibration with anaesthesia group, the difference in mean body weight was also significant ($p<0.05$ by X2 Test). These results indicate that anaesthesia had an adverse effect on body weight.

Tissue perfusion

Tissue perfusion was measured using Laser Doppler. The tissue perfusion in rat tail arteries was measured using BLF 21 Laser Doppler apparatus (Transonic System, Inc.) coupled to a Gould Brush 220 chart recorder. The Doppler probe was recessed in the vibrating platform to provide a level surface for the tail and positioned against the ventral surface of caudal tail segment C7. After 5 minutes of treatment the tissue perfusion results were as follows. Tissue perfusion in the anaesthesia group was obviously decreased compared with normal rats due to vasodilation and heart beat decrease. The tissue perfusion of the vibration with anaesthesia group was similar but slightly greater than the anaesthesia group. The tissue perfusion in the vibration without anaesthesia group was obviously decreased. For all rats, a baseline TPU was recorded before a 5-minute period of no treatment for the control and a 5-minute period of 5g vibration at 60 Hz vibration for the vibrated rat. The polygraph was stopped during vibration of the test rat and during a 1-hour post-vibration waiting period. TPU (Tissue Perfusion Units) was unchanged in control rats throughout the test period. The vibrated rat exhibited decreased TPU after 5 minutes of vibration and increased TPU one hour later. Figure 3 shows the TPU readings for control (non-vibrated) rats and rats vibrated without anaesthesia.

Results of Pathohistology Study (specimens from Models II and III)

Light microscopic study on the tail artery revealed the following lumen area changes after one hour: There was no change in the normal control, which had received no treatment. The lumen area was in-

Table 2. Rat's body weight change. Weight expressed in grams; n = 10

	Normal	**Anesthesia**	**Anesthesia & Vibration**	**Vibration**
1 day	200.8 ± 6.8	218.3 ± 7.7	222.1 ± 9.7	221.6 ± 9.8
9 days	254.3 ± 9.9	224.9 ± 10.4	243.8 ± 116	253.4 ± 12.0
Weight increase	+53.5	+6.6	+21.7	+31.8
Percentage increase	26.6%	3.0%	9.8%	14.4%

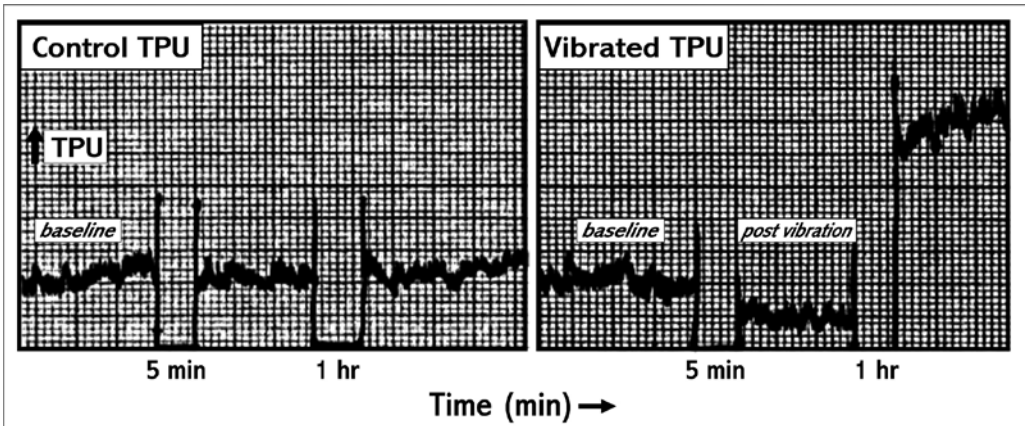

Figure 3. Laser Doppler tissue perfusion unit (TPU) comparison. Baseline before tail vibration (left). Polygraph was paused 5 minutes during vibration and 1 hour afterward. TPU, unchanged in control, was decreased in test rat after 5-min. vibration and increased 1 hour later.

creased in the sham control group, which received anaesthesia but no vibration. In the vibration with anaesthesia group, there was either no change or a slight increase in lumen area. In the vibration without anaesthesia group, there was a strong decrease in lumen area.

TEM (Transmission Electron Microscopy) study was performed with focus on endothelial cells. Rats in the normal control group (without any treatment) showed no change. Rats in the anaesthesia (sham control) group showed vessel dilation and some blood cell stasis on wall. Rats in the tail vibration with anaesthesia group showed no change (See Fig. 4A). Rats in the tail vibration without anaesthesia group showed strong spasm, multiple folding of endothelium, and squeezing of endothelial cells (See Fig. 4B).

General Observations

In all models, we observed animals with respect to the following criteria: behaviour toward restraint devices, self-grooming behaviour as shown in appearance of coat, secondary complications such as haematuria and porphyrin discharge (chromodacryorrhea), heart rate, body temperature, and growth rate as measured by increase in body weight. Table 3 contains a summary of our observations.

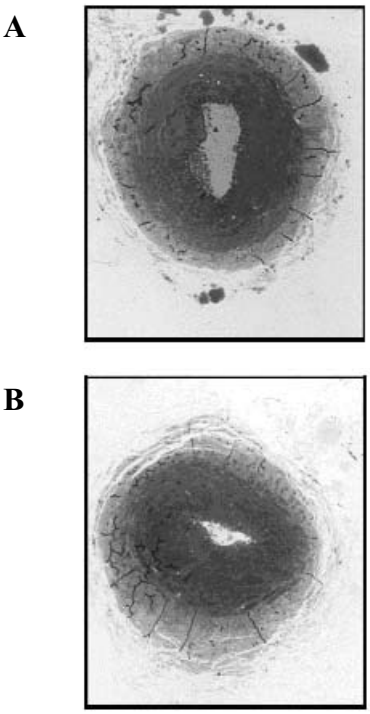

Figure 4. Semithin (0.5µm transverse section of rat-tail artery in the (A) sham control group and (B) vibration group (vibration 6 hrs/day x 9 days). Lumen area was clearly decreased.

Table 3. General observations of vibrated animals' condition in various models [N = 20 for each model]

Model Type: / Criterion:	Vibrated Rat Leg with Anesthesia	Vibrated Rat Tail with Anesthesia	Vibrated Rat Tail without Anesthesia (minimal restraint cage)
Behavior	80% (16) Animals showed signs of moderate stress (e.g., clenching, biting, clawing fixation tapes, shaking)	80% (16) Animals displayed signs of mild stress: clawing but no biting.	Animals showed no signs of stress. They appeared calm in restraint devices and had only a brief startle response to vibration.
Unkempt Appearance of Coat	100% (20)	100% (20)	0% (0)
Decreased Weight Gain	80% (16)	70% (14)	0% (0)
Complications	25% (5) had hematuria	No hematuria.	No hematuria.
	80% (16) had chromodacryorrhea	No chromodacryorrhea.	No chromodacryorrhea.
Heart Rate	Decreased	Decreased	Normal
Body Temperature	Decreased an average of 3.8°C	Decreased an average of 3.8°C	No change.
Growth rate, measured by weight gain *	<3% growth rate	9.8% growth rate	11.7% growth rate

*Normal growth rate is 26.6%

Discussion

Effect of anaesthesia in animal model

Anaesthesia affects the normal physical environment and results in physiological changes that are not only detrimental to experimental animals but can also alter experimental data. In the anaesthesia groups, the heart rate decreased. Vasodilation and venous stasis due to blood staying in the venous pool significantly affected tissue perfusion. This is typical of vibration-induced white finger syndrome, in the early stages of which vibration produces vasospasm. In our study, in the anaesthesia stage, vasodilation is contrasted with vasospasm. For this reason, anaesthesia interferes with accurate study results. Furthermore, in anaesthesia groups, the animals' food intake was decreased, and they appeared lethargic for longer periods after the procedures. There was a decrease in weight gain, their body condition was poor, and their normal physical activities were affected. This affected all neural and vascular physical states and eventually affected all study results. Using intraperitoneal anaesthesia, al-

most all animals in vibration groups needed another injection one hour after the previous injection. This additional injection was effective for 45 minutes to one hour. Each additional injection carries additional risk of injury to intra-abdominal organs. For example: hepatic hematoma, intestinal hematoma, bladder hematoma, and haematuria may result. In addition, these injections interrupted the vibration testing, altering the test conditions. For these reasons, and because it most closely resembles the human work state, the group without anaesthesia is the ideal model for animal study.

Regarding the vibrated part of the body

Porphyrin secretion and haematuria were seen in vibrated hind leg groups but not in the vibrated tail groups. This difference may be attributable to the presence or lack of vibration transfer to the whole body or to stress reaction. In Model II, we used rat tail for vibration to replace vibrated hind leg. It made a great difference. The difference was that in rats, the thigh has numerous and broad tissue connections to the body (*Olsen and Neilsen, 1988; Bovenzi, 1998; Noël, 2000; Palmer et al., 2000; Lindsell and Griffin, 1999; Kennedy et al., 1999; Bovenzi et al., 1997; NIOSH, 1989; Wasserman, 1987; Harada et al., 1999; Bovenzi et al., 1999; Bovenzi et al., 2000-a; Färkkilä et al., 1988; Hagberg et al., 1991; Sakakibara, et al., 1988; Taylor, 1986; Bovenzi et al., 1991; Bovenzi et al., 1994*). We cannot supply vibration only to the leg without vibrating the body. The vibration transfers to the body, making the whole body vibrate. This interacts with the leg vibration and makes it difficult to focus on the vibrated part. To study the pathology, we have to focus on a certain part to study the vessels and neuropathohistological changes. In Models II and III, we used the rat tail for vibration. The rat tail is a long part with much less tissue connection to the body. It is easy to provide vibration on only one part and focus on small tissue study. In the rat tail the ventral artery is ideal for vessel study. The diameter is very close to the diameter of the artery in a human finger. The ventral artery diameter is about 0.6 to 1.3 mm. There are four tail nerves, two on the dorsal and two on the ventral side (Fig. B). The diameter of these nerves is also very close to the diameter of human finger nerves. Also, there are numerous muscles and tendons that can also be used in vibration study.

Compliance with the "Guide for the Care and Use of Laboratory Animals"

One concern is that without anaesthesia, rats may become distressed from restraints or vibration. However, the test used in Model III has been performed many times, and rats seem to have a preference for the tubular restraint device and readily enter it when presented. The head, limbs, and body can move freely except for the tail. Isolating the vibration part appears to bring less stress to the animal. All vibrated rats in this model (Model III) appeared to be calm and less stressed than in the older model.

Conclusions

Vibration without anaesthesia

Vibration without anaesthesia is an ideal condition for vibration study because there is no added interference in the normal physiological state that could alter testing results.

Rat tail without anaesthesia is an ideal organ for vibration study

Investigators can provide concentrated vibration in isolation from the animal body. Rats can stay calmly in a small restraint device for long hours without any anaesthesia, with only the tail subjected to vibration.

Abbreviations used in article

HAVS	Hand-Arm Vibration Syndrome
VWF	Vibration-induced White Finger
PVC	Polyvinyl chloride
Hz	Hertz
G	force equivalent to that of gravity
B&K	Bruel and Kjeer
°C	degrees Celsius [Centigrade]

TEM	Transmission Electron Microscopy
mm	millimeters
cm	centimeters
m/s^2	meters per second squared

Acknowledgments

The authors are grateful for the assistance of Beth Kaczmarek, editorial consultant for the Department of Plastic Surgery at the Medical College of Wisconsin, in the preparation of this manuscript.

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