VIBRATION ENHANCEMENT OF BLOOD-ARTERIAL WALL MACROMOLECULE TRANSPORT*

R. M. Nerem

ABSTRACT

The influence of low-frequency, high-intensity, whole-body vibration on blood—arterial wall macromolecule transport has been investigated for ^{131}I-albumin. In vivo studies of ^{131}I-albumin uptake in the canine aorta during whole-body vibration have been carried out in anesthetized animals at a frequency of 10 Hz and with a peak-to-peak amplitude of 1.27 cm. These measurements, when compared with control measurements, indicate that during vibration there is a significant alteration in the pattern of albumin uptake in the aorta, together with an increased rate of uptake along its entire length. In vitro studies have investigated the influence of sinusoidal pressure and flow variations on the transendothelial transport of albumin in serum perfused excised dog common carotid arteries. These results suggest that it is the vibration-induced arterial wall shear stresses and a shear dependent transport process that are responsible for the enhancement of albumin uptake by the aortic wall during whole-body vibration.

INTRODUCTION

This paper addresses itself to the role of hemodynamics in arterial disease processes during laboratory-induced vibration. Such a hemodynamic influence is in all probability mediated through the pressure force and/or the wall shear or frictional force acting on the arterial wall. These forces are illustrated in Figure 1. Pressure has long been considered a possible

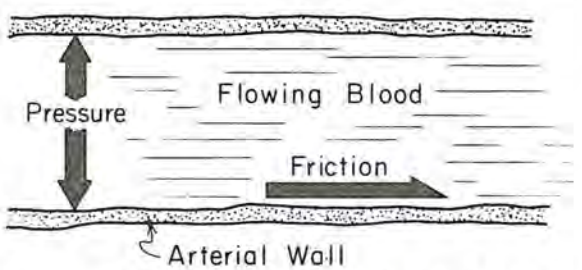

Figure 1. Illustration of hemodynamic forces acting on arterial wall.

mechanistic agent in arterial disease because of the recognition of hypertension as a risk factor. However, more recently the wall shear stress also has been identified as being an important aspect of a blood flow–arterial wall interaction phenomena. If anything, it is this latter force component that will be emphasized in this consideration of whole-body vibration effects.

*Supported by the Air Force Office of Scientific Research under Grant 73-2526.

SHEAR DEPENDENT PHYSIOLOGICAL PROCESSES

There is increasing evidence that the transport of blood elements to the arterial wall is influenced by hemodynamic forces and, in particular, by the level of the wall shear stress. There is also evidence that if the wall shear becomes sufficiently elevated, endothelial damage may occur. If one couples this knowledge with the fact that (a) vibration may produce significant alterations in flow properties and that (b) in some studies of Raynaud's phenomenon there have been reports of arterial occlusion in subjects who used some type of vibrating tool in their work, it would seem appropriate to examine more closely the possible role of vibration-induced changes in hemodynamics.

Because of the large variations in wall shear stress that can occur in the arterial system and because certain vascular sites seem preferentially to develop arterial disease, a number of investigators have studied the possible relationships and interactions that might potentially take place. An early qualitative picture of this was presented by Fry based on a series of in vivo experiments,[1] and this is summarized in Figure 2. These results indicate that for wall shear stress levels

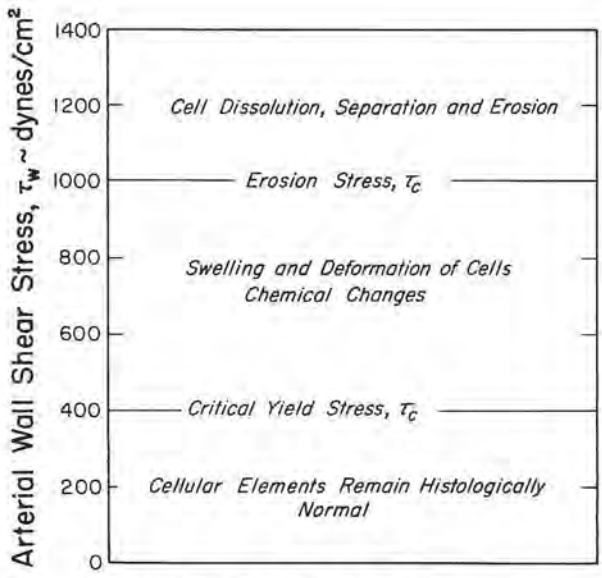

Figure 2. Relationship of endothelial changes to arterial wall shear stress.

below a certain critical yield stress value, the endothelial cellular elements remain histologically normal. In this subcritical yield stress range, however, variations in shear stress may still influence the rate of transport of certain blood elements.[1-3]

Exceeding the critical yield stress level, the endothelial cells begin to yield, deform, and swell slightly (Figure 2). Fry noted that the cells had significantly altered staining properties indicative of chemical changes. In this range, transport is also enhanced by increasing wall shear stress. Finally, as further increases in wall shear and the erosion stress of the endothelial cells is exceeded, Fry noted the denudation of endothelial cells, invasion and deposition of lipid material, adherence of cellular elements, and deposition of fibrin.

Reference 1 quotes a value for the critical yield stress of approximately 400 dynes/cm² and for the erosion stress, a value of 1,000 dynes/cm². Both of these stress levels would be expected to be dependent—possibly highly dependent—on a number of physiological and environmental factors. Thus, the values quoted here should only be considered as representative, and for the conditions frequently associated with the occurrence of Raynaud's phenomenon of occupational origin, the critical yield stress and the erosion stress levels could be considerably different from the above noted values.

VIBRATION-INDUCED ARTERIAL FLOW CHANGES

With this background concerning the influence of wall shear stress on physiological processes, one next must consider the possible enhancement of hemodynamic forces by whole-body vibration. Studies have been carried out in our laboratory on the influence of whole-body sinusoidal vibration (applied along the axis of the spinal cord) on the pressure and velocity waveforms in the canine descending thoracic aorta.[4,5] These exploratory studies have been at a frequency of 10 Hz and with a peak-to-peak amplitude of 1.27 cm. Pressure waveform measurements indicate that the influence of whole-body vibration is largely to produce a sinusoidal pressure wave of the same frequency as the vibration and with an amplitude of less than 5 mm Hg, which is superimposed on the normal aortic pressure waveform. Hot-film anemometer velocity measurements, on the other hand, indicate that the influence of whole-body vibration is to produce a sinusoidal velocity wave with a peak-to-peak amplitude of 30 cm/sec, which is superimposed on the normal aortic velocity waveform. These values may be compared with normal nonvibration values of 100 mm Hg for mean arterial pressure, a pulse pressure of 40 mm Hg, a mean velocity of 15 cm/sec, and a peak systolic velocity of 100 cm/sec. Furthermore, the measured vibration-induced velocity amplitude of 30 cm/sec allows one to estimate an associated induced peak wall shear stress value of approximately 25 dynes/cm². This may be compared with a mean aortic wall shear stress of 10 dynes/cm² and a peak aortic wall shear stress under nonvibration conditions of 100 dynes/cm². Although these comparisons are no more than suggestive, when they are considered with the in vitro ^{131}I-albumin uptake experiments to be discussed later, there is an indication that vibration-induced wall shear stresses may be more important than vibration-induced pressure oscillations when considering the blood flow — arterial wall interaction. However, this must be taken to be only a very tentative conclusion.

IN VIVO STUDIES

To investigate whether or not whole-body vibration does indeed influence blood–arterial wall macromolecule transport, in vivo measurements of ^{131}I-albumin uptake in the canine aorta have been carried out in anesthetized animals. In this, the animal is vibrated along the axis of its spinal cord at a known frequency and amplitude. During vibration, the cardiac output is measured using the dye dilution technique, and labeled albumin is injected and allowed to circulate for the desired time interval. The animal then is sacrificed and the aorta excised and sectioned into appropriate samples. Although wall shear stress was not determined explicitly in these in vivo experiments, an estimate of the mean wall shear stress in the ascending aorta indicates a value on the order of 10 dynes/cm². However, as noted previously, the peak shear stress values associated with the pulsatile aortic flow would be considerably higher. Nonvibration, control experiments were carried out as well as experiments where the animal was exposed to whole-body vibrations at frequencies of 6, 10, and 14 Hz, and with a peak-to-peak amplitude of 1.27 cm.

Data from these experiments were normalized using

as a parameter the amount of ^{131}I-albumin accumulated in each sample per unit surface area per unit time divided by the time-averaged concentration of ^{131}I-albumin in the blood. This quantity is designated as $\dot{m}/C_0$ with the units of (net counts ^{131}I-albumin/cm^2-sec)/(net counts ^{131}I-albumin/ml blood); it was chosen because, if the blood concentration is considered the driving force in the wall uptake process, then its use allows measurements from different experiments to be readily compared. The units on the mass flux parameter, $\dot{m}/C_0$, are those of a velocity (cm/-sec). This is the tracer or wall permeability, and it is the characteristic velocity of the wall uptake process.

Some results obtained in this series of in vivo experiments are presented in Figure 3. Included here

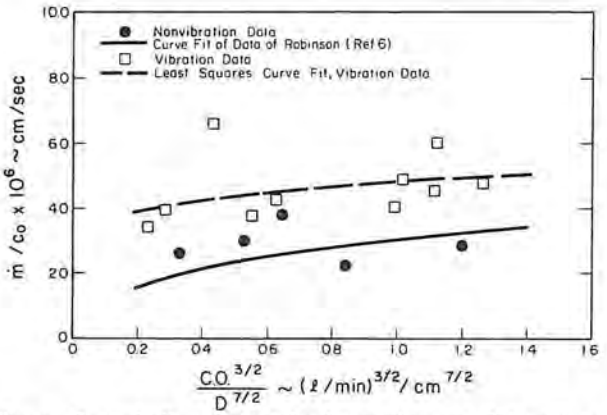

Figure 3. ^{131}I-albumin uptake by canine arterial wall at posterior ascending aorta site as a function of shear stress parameter for nonvibration and vibration at 10 Hz and a peak-to-peak amplitude of 1.27 cm.

are only data from the posterior ascending aorta position. Shown are control data obtained under nonvibration conditions, a curve fit of the previously obtained nonvibration data of Robinson et al.,[6] the present vibration data, and the curve fit of the vibration data. The ordinate is the previously introduced parameter, $\dot{m}/C_0$, and the abscissa is the parameter C.O. $^{3/2}/D^{7/2}$, where C.O. is cardiac output and D is aortic diameter. As is shown in reference 5, this parameter is representative of the mean wall shear rate. It may be seen that the present control data are in reasonable agreement with the curve fit of Robinson's data.[6] The vibration data, on the other hand, represent on the average a factor of two higher values for the wall uptake parameter, $\dot{m}/C_0$. This is consistent with the idea of whole-body vibration inducing alterations in arterial blood flow, including wall shear stress, and a shear dependent blood arterial wall transport process.

This study has recently been extended to include vibration frequencies of 6 and 14 Hz. These results are summarized in Figure 4 for the relatively low cardiac outputs and where the vibration peak-to-peak

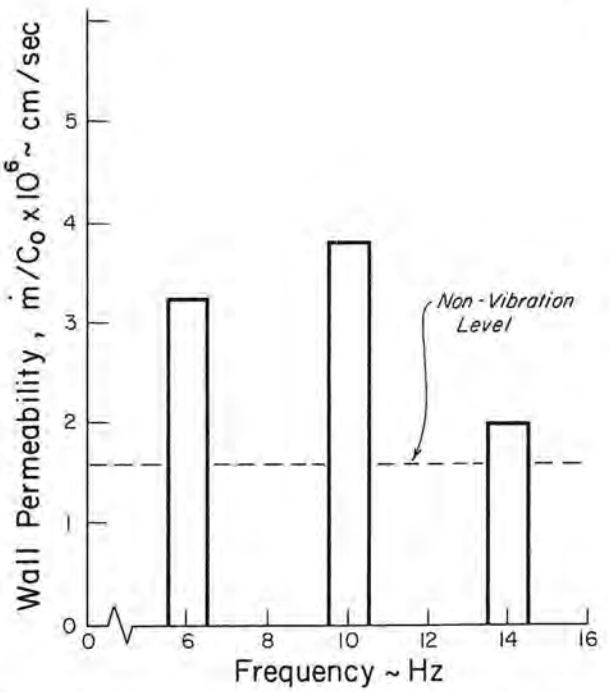

Figure 4. ^{131}I-albumin uptake by canine arterial wall at posterior ascending aorta site for low cardiac outputs and as a function of vibration frequency and for a peak-to-peak amplitude of 1.27 cm.

amplitude is 1.27 cm for all frequencies. As may be seen, at both 6 and 10 Hz, there is considerable vibration enhancement of wall uptake when compared with the indicated nonvibration level. However, at a frequency of 14 Hz, there is virtually no influence of whole-body vibration, and this may be due to relatively poor coupling of the vibration into the animal at that frequency.

It also should be noted that the uptake of albumin in the arterial wall occurs not only across the endothelium, but also through the vaso vasorum. Thus, although pressure and velocity measurements can predict the effect of vibration on the aortic flow properties, the effect of vibration on the microcirculation and on albumin uptake due to this mechanism are not known. It is certainly not totally unreasonable, however, to suspect that whole-body vibration could alter the fluid mechanics and albumin transport associated with the microcirculation. This would, of course, be a mitigating factor in the interpretation of the present results.

Also of interest is the influence of whole-body vibration on the spatial distribution of albumin uptake along the canine aorta. Shown in Figure 5 is the average, over a large number of experiments, of the measured albumin uptake at a particular indicated sample site divided by the value of uptake in the posterior ascending aorta sample. Presented are both control, nonvibration values as well as values obtained during whole-body vibration at 10 Hz and

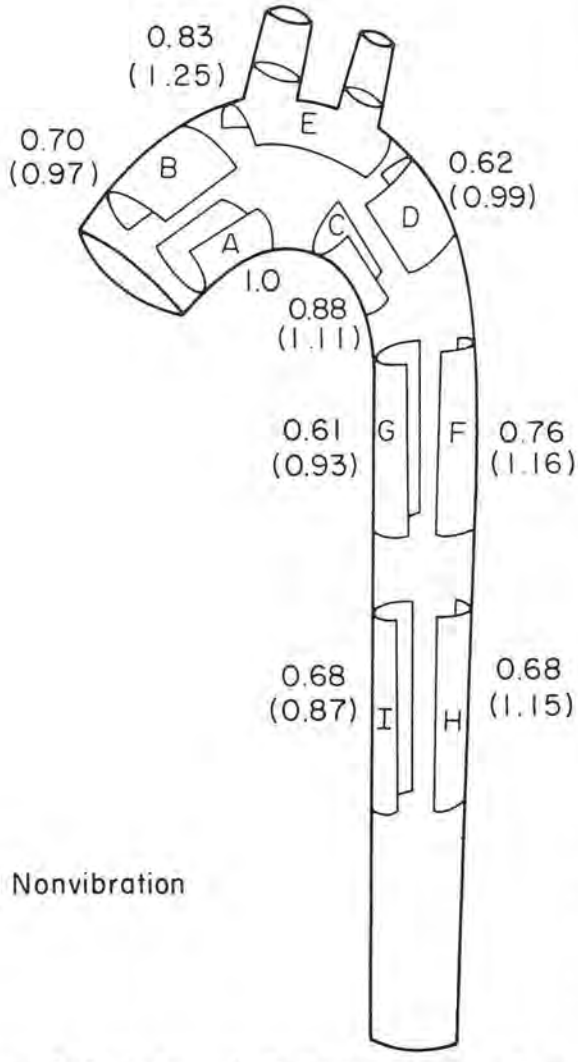

Figure 5. Comparison of distribution of averaged uptakes along canine aorta for nonvibration and vibration at 10 Hz and a peak-to-peak amplitude of 1.27 cm. Values given are the average mass flux of ^{131}I-albumin at the indicated site normalized with respect to the average mass flux at the posterior ascending aorta site.

with a peak-to-peak amplitude of 1.27 cm. As may be seen, there is a definite shift in the spatial distribution in the presence of whole-body vibration. Recent experiments at 6 and 14 Hz (still in progress) show a similar trend, and thus not only is the level of uptake influenced by a whole-body vibration, but also the spatial distribution.

IN VITRO STUDIES

To further investigate the role of flow oscillations in the transport of macromolecules between blood and the arterial wall, a series of experiments have been carried out that involve the in vitro measurement of albumin transport between serum and the wall of an excised dog common carotid artery in the presence of a purely oscillatory flow, i.e., where there is no mean flow, as illustrated in Figure 6. The os-

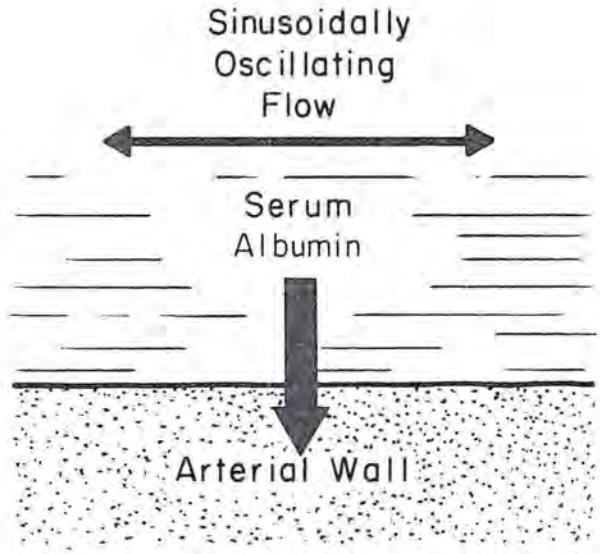

Figure 6. Illustration of in vitro experiment in which excised artery is exposed to sinusoidally oscillating serum containing ^{131}I-albumin and where there is no mean flow.

cillatory motion in this case is produced by a roller pump mechanism acting on a silicone tube; the other accessories, e.g., water bath, heater, saline pan (in which the artery is mounted), and air pressure reservoir (for maintaining a mean arterial pressure of 100 mm Hg), are similar to those of reference 2. In these experiments, the oscillation frequency ranged from 1 to 4 Hz and the half-amplitude of the roller displacement, from 1 to 3.5 cm. Using the calculations of reference 7, the peak shear stress ranged up to over 100 dynes/cm^2 and the root mean square wall shear stress up to 75 dynes/cm^2.

The results from these in vitro oscillatory flow perfusion experiments are shown in Figure 7 in the form of $\dot{m}/C_0$ as a function of peak wall shear stress. These preliminary measurements show a shear dependence which appears to be relatively independent of frequency and half-amplitude (since generation of the same wall shear stress at two different frequencies requires two different half-amplitudes). For data obtained at a peak wall shear stress of less than approximately 50 dynes/cm^2, a least squares fit indicates that $\dot{m}/C_0$ depends on shear stress to the 0.5 power. This weak dependence is consistent with previous steady state in vitro perfusion results.[2] Above 50 dynes/cm^2, there appears to be a somewhat stronger shear dependence although more data are required to quantify this trend. However, should this prove to be true, this would be consistent with the results of Carew[3] as well as with the more recent results of Reif et al.[8] in which the steady state in vitro perfusion

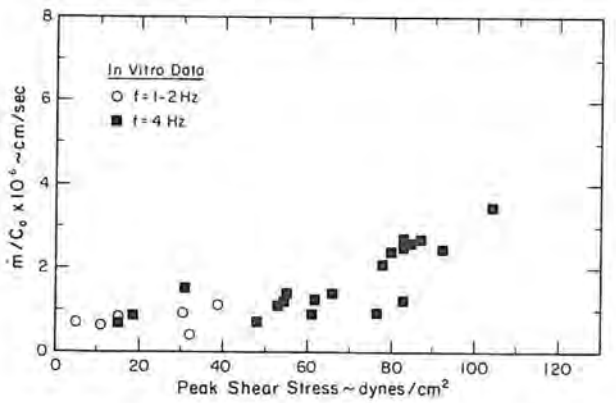

Figure 7. ^{131}I-albumin uptake by arterial wall as a function of peak wall shear stress for excised dog common carotid arteries in the presence of sinusoidally oscillating flow.

studies noted earlier are being extended to higher shear stress levels.

The purpose of the apparatus used in this series of experiments was to produce an oscillating flow while at the same time minimizing any pressure oscillations. However, for the fluid to be accelerated and decelerated, a pressure gradient must be produced, and this will necessarily result in some pressure oscillations. Thus, as a corollary to the in vitro oscillatory flow experiment described here, a limited number of experiments are now being carried out in which the uptake of albumin in an excised carotid artery is being measured under conditions of virtually no flow, but where there are finite pressure oscillations.

These data, which are very preliminary in nature, indicate a relatively small increase in albumin uptake with increasing pressure amplitude. As an example of the effect of pressure oscillations, the uptake of albumin in the presence of a ± 50 mm Hg pressure oscillation at 1 Hz and with a mean pressure of 100 mm Hg is approximately 5×10^{-7} cm/sec; this may be compared with a value of $\dot{m}/C_0 = 3 \times 10^{-7}$ cm/sec for no flow and a constant pressure of 100 mm Hg. However, pressure oscillations may be an important factor in the data scatter found at the higher shear stresses in Figure 7, since the pressure oscillations have the greatest amplitude at conditions resulting in the higher shear stress levels and may serve to violate endothelial integrity.

A similar series of experiments are now being carried out using ^{14}C-4-cholesterol. Initial results indicate a similar wall shear stress dependence with values of $\dot{m}/C_0$ being quite comparable for ^{131}I-albumin and ^{14}C-4-cholesterol.

CONCLUSIONS

These in vivo and in vitro results are consistent with an interpretation based on shear-dependent mass transfer process and with the earlier hypotheses relating to Raynaud's disease.[9] More importantly, however, the results demonstrate how flow oscillations, whether induced by vibration or not, can influence a rather basic aspect of wall physiology such as blood–arterial wall transport processes. Whether this is purely a wall shear stress effect or whether pressure pulsations also play a role cannot be decided at this time. However, it is clear that hemodynamic effects must be included in a detailed consideration of blood-arterial wall macromolecule transport and that there may be implications of significance in problems involving whole-body vibration.

REFERENCES

1. Fry, D. L.: Certain histological and chemical responses of the vascular interface to acutely induced mechanical stress in the aorta of the dog. Circ. Res. 24:93-108, 1969.
2. Caro, C. G., and Nerem, R. M.: Transport of ^{14}C-4-cholesterol between serum and wall in the perfused dog common carotid artery. Circ. Res. 32:187-205, 1973.
3. Carew, T. E.: Mechano-chemical response of canine aortic endothelium to elevated shear stress in vitro. Thesis, Catholic University of America, Washington, D. C., 1971.
4. Hay, G. D., Nerem, R. M., and Hamlin, R. L.: Low-frequency wholebody vibration effects on pulse wave propagation. Proceedings of the 25th Annual Conference on Engineering in Medicine and Biology 25:217, 1972.
5. Schwerin, W. D.: Effects of low frequency, high intensity, wholebody vibration on the uptake of ^{131}I-albumin in the canine aorta. M. S. Thesis, The Ohio State University, Columbus, Ohio. 1974.
6. Robinson, D. L., Nerem, R. M., and Carey, W. E.: An in vitro study of the shear dependence of albumin uptake in the canine aorta. ASME Biomechanics Symposium AMD-2:23-24, 1973.
7. Ling, S. C., Atabek, H. B., Fry, D. L., Patel, D. J., and Janicki, J. S.: Application of heated-film velocity and shear probes in hemodynamic studies. Circ. Res. 23:789-801, 1968.
8. Reif, T., Nerem, R. M., and Kulacki, F. A.: An in vitro study of transendothelial albumin transport in a steady state pipe flow at high shear rates. ASME J. Fluids Engr. (Accepted for publication).
9. Nerem, R. M.: Vibration-induced arterial shear stress: The relationship to Raynaud's phenomenon of occupational origin. Arch. Environ. Health 26:105-110, 1973.

QUESTIONS, ANSWERS, AND COMMENTARY

Question (J. Lafferty, University of Kentucky): You did avoid commenting on potential mechanisms. One thing you didn't mention was the potential effect of turbulence because mixing will obviously enhance the driving force or the diffusion. To what extent do you believe, based on your present study, that turbulence may contribute substantially to this effect?

Answer: Well, there are really two questions involved here; first, is turbulence present? I think in these animal studies turbulence is not present. Generally when you take a dog and give it anesthesia, you drive it away from its normal condition; you drive it to a lower Reynold's number. As far as our measurements with hot-film aneomometers would

indicate, the flow is not turbulent. That doesn't mean it's not turbulent under normal physiological conditions.

If turbulence is there in the normal physiological system (and I would probably say it is present in the aortic arch region, although not necessarily in the abdominal arch region if you are talking of normal physiological conditions), then, the second part of the question becomes, what is the role of that turbulence? Turbulence would enhance the diffusion but that probably is not important. The diffusion across the blood to the wall is inconsequential as a rate-limiting factor in these transport processes. The rate-limiting factor is the mechanism by which those molecules get taken up into the wall, and there has been considerable attention lately given to the other types of transport processes as opposed to simple diffusion processes. The turbulence possibly could play a role in the sense that one would expect a higher stress on the wall if the flow is turbulent than if it is laminar, and so it could contribute to the stress in that manner—not in terms of a mixing phenomenon but in terms of an enhanced stress on the wall.

Question (H. Von Gierke, Aerospace Medical Research Laboratory): In your whole-animal experiments, you must count on considerable deformation of the arteries by the external forces, particularly in the region classified as part "A" in the aortic arch. Now I assume that this deformation of the wall may influence the transport velocity. Did you exclude such wall deformation in your in vitro experiments?

Answer: In the in vitro experiments, the vessels were free to distend. It's not clear that they underwent the same type of deformation as the vessel during the whole-body vibration conditions. As far as the whole-body experiments are concerned, probably in the aortic arch region there is much more distortion of the vessel than, say, in the abdominal region. This may end up explaining or at least be a major factor in the change in the nondimensional pattern. That I would be perfectly willing to accept.

Question (H. Von Gierke): But you did not exclude this mechanism in the in vitro experiments?

Answer: The vessels were not constrained; they were free to move, to distend radially. We have done some experiments using steady pressure, and basically in those experiments (where we haven't gone as high in pressure as we should have), we've been up to 140 to 150 mm Hg. That's not really a case of hypertension, but in those studies we found that the pressure level is only important in terms of distending the vessel and changing the available surface area. And if we correct for available surface area, we can collapse all our data for pressures from 10 to 150 mm Hg on one curve.

Question (H. Von Gierke): Yes, but if you do your in vitro experiments and you do them with pressure and not flow, that would more or less suppress normal wall deformations?

Answer: It depends on what kind of deformation you are talking about. If you do it with pressure oscillations and no flow, you still get the radial distension but you don't get the longitudinal type of distension.

Question (H. Von Gierke): You won't get, at the higher frequencies, large curvature in the muscles, and that's where your change in transport exists?

Answer: That's correct.

Question (F. Dukes-Dobos, NIOSH): I wonder whether we can ask you to give us your own ideas concerning these results and some theory of development of either Raynaud's disease or arteriosclerosis?

Answer: (W. Taylor, University of Dundee): Could we just look at Raynaud's and the work of Lewis and others? They have described that the intima is the first of all at fault, and then the medial coat undergoes hypertrophy, and then, finally, the medial coat collapses under long vibration and up comes the adventitia again. Following on that same question, it's strange to us that in the sensitivity region, where there is blanching when we take out the sections, it's the medial coat which is hypertrophied, and the lining coat is intact as far as we could tell. All this is highly relevant to the future and if anybody else has got any ideas on the pathology we would love to hear them to help Dr. Nerem in what is a huge extension of his animal work. I would like to ask Dr. Nerem why he goes down so low in frequency and doesn't come up to a 100 Hz? Would you like to answer that? Have you done any work higher than 10 Hz?

Answer (R. Nerem): We've been up to 14 Hz. That's as high as we've been and that's because of the mechanical limitations of our present system. It was a good place to start because we had the system in-house and it was working. One of the things we are interested in is going to higher frequencies because I am sure that if you talk about a frequency response curve for the endothelium, in terms of sensitivity, that it's going to be markedly different at some frequencies than others. To get back to your question, I'm not sure I can really answer it. I was interested by some of the comments made earlier because you get into the question of, is the disease just one in terms of hand sensitivity or are there in fact vascular changes? I think probably the kind of ideas I've given here fit in better with the viewpoint of vascular changes. Moreover, chemistry is vital since, when you are talking chemistry, you are talking about material that has to be supplied to go into chemical reactions, and if you can influence transport rates, then you can influence wall chemistry. So even though, for example, in terms of Dr. Taylor's comments, even though the endothelium may be rate limiting this thing, the hemodynamics enter in through the force applied to the endothelium, thus influencing the transport rate. Those molecules, once in the wall, go to the intima. It may be there that you actually get the biochemical changes, and this may be why you see that as the major effect as opposed to endothelial changes.

Question (A. Zweifler, University of Michigan): Do you think it's fairly possible to do work where

you combine what you are doing with some kind of direct observation of the cells? Some pathologic correlation, say with an electron microscope? Do you think that there might be changes in the endothelial cells that might occur, as you implied they might? Some effect of shear when you've also got some biochemical change in the cells that you've induced by having materials transported into the cells because of the stress that you put them under? In other words, will there be changes that you can observe directly under a microscope?

Answer: I don't know the answer to that question. We have some pathologists working with us who have done some very crude pathology and histology. I think we need to do more in this area, but I can't answer as to whether we really would be able to see something. So far, the crude pathology that's been done doesn't show any real difference for these conditions. But you know we are speaking of a very short duration type event. So it's not clear that the pathological changes should manifest themselves. That would be an entirely different type of study where you expose an animal, or whatever the subject is, to a long-term condition and look for the histological changes. It's not clear that we ought to see anything from 15 minutes of what we are doing.

Question (A. M. Ehrly): I think it is very difficult to compare your results to the situation in Raynaud's disease. There are very different types of arterial vessel walls. We have the influence of the platelets in this region. We have other wall shear stresses, and I think one should think about the influence of the so-called fibrinogen layer in the small vessels, which may not play a role in the aorta but in the smallest arterioles. Do you have any idea about the influence of the fibrinogen layer, which covers the endothelium, in your experiments?

Answer: Well, I appreciate your comment. I certainly agree that it is hard to tie this into disease. This is why I tried to avoid it. On the other hand, I think probably, to ultimately reach an understanding on what is going on in the disease, we need to know more about the basic processes and not just have epidemiological type data.

PROCEEDINGS OF
THE INTERNATIONAL OCCUPATIONAL HAND-ARM VIBRATION CONFERENCE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

PROCEEDINGS OF
THE INTERNATIONAL OCCUPATIONAL HAND-ARM VIBRATION CONFERENCE

Sponsored by
National Institute for Occupational Safety and Health
Cincinnati, Ohio, U.S.A.
October 1975

Editors:
D. E. WASSERMAN
W. TAYLOR

Manuscript Editor:
M. G. CURRY

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
Cincinnati, Ohio 45226
April 1977

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

DISCLAIMER

The sponsoring of this symposium and publication of this proceedings does not constitute endorsement by the National Institute for Occupational Safety and Health of the views expressed or recommendation for any commercial product, commodity, or service mentioned herein.

DHEW (NIOSH) Publication No. 77-170