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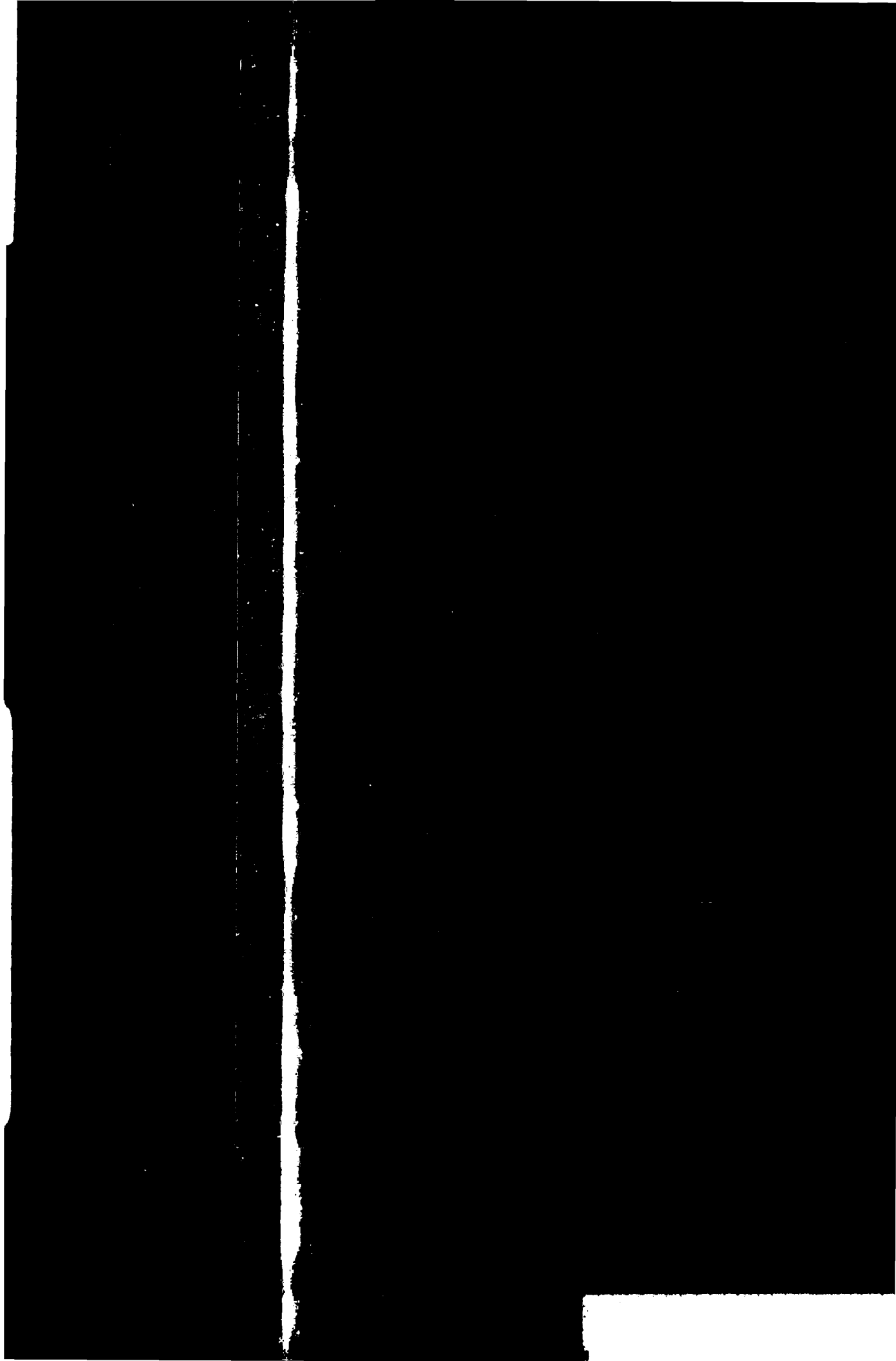
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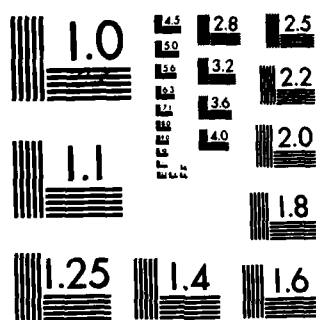
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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO. AD-A143 752	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) FINAL REPORT: The Effects of Middle Ear Pressure on Hearing		5. TYPE OF REPORT & PERIOD COVERED Final Report November 1982 - October 1984
7. AUTHOR(s) CLOPTON, Ben M., Ph.D.		6. PERFORMING ORG. REPORT NUMBER
9. PERFORMING ORGANIZATION NAME AND ADDRESS Department of Otolaryngology RL-30 School of Medicine University of Washington, Seattle, WA 98195		8. CONTRACT OR GRANT NUMBER(s) ONR contract # N00014-75-C-0463
11. CONTROLLING OFFICE NAME AND ADDRESS Department of the Navy, Office of Naval Research, 800 N. Quincy Street, Arlington, VA 22217 Code 441NP		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) Office of Naval Research, Room 315 University District Building, JD-16, 1107 NE 45th Street, Seattle, WA 98195		12. REPORT DATE 30 April 1984
		13. NUMBER OF PAGES 9 plus appendix
		15. SECURITY CLASS. (of this report) unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;">This document has been approved for public release and sale; its distribution is unlimited.</div>		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report) <div style="text-align: right; font-weight: bold; font-size: 1.2em;">DTIC ELECTE JUL 27 1984</div>		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) hearing, cochlear function, barotrauma, noise exposure, middle ear pressure		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This is the final report of the last contract in a program of research on the effects of middle ear pressure on hearing. It primarily lists publications and presentations resulting from this program of research.		

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S/N 0102-LF-014-6601

unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

84 05 31 096

DEPARTMENT OF OTOLARYNGOLOGY  
UNIVERSITY OF WASHINGTON  
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TO: Department of the Navy  
Office of Naval Research  
Code 441NP  
800 N. Quincy St.  
Arlington, Virginia

TITLE: Final Report: "Effects of Middle  
Ear Pressure on Hearing"  
ONR contract #N00014-75-C-0463

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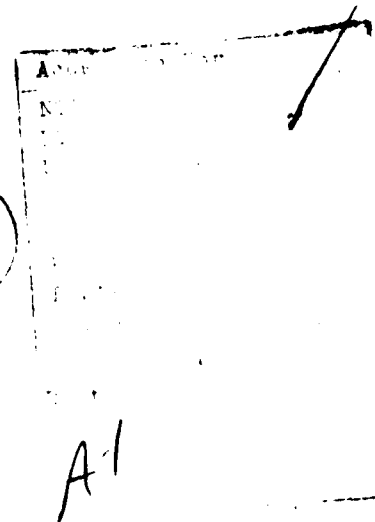
PROJECT PERIOD: 1 November 1982 - 31 October 1984  
(incl. 1 year extension)

PERFORMANCE SITE: School of Medicine  
University of Washington  
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UNIVERSITY OFFICIAL FOR  
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DATE: 26 April 1984



## TABLE OF CONTENTS

	<u>Page</u>
I. Introduction	1
II. Final Progress Report	2
III. Publications and Presentations Resulting from ONR Contract	5
IV. Appendices	

FINAL REPORT\*

The Effects of Middle Ear Pressure on Hearing

I. Introduction

This is the final report for ONR contract #N00014-75-C-0463 which is being terminated 30 April 1984. This research is the last in a series of projects extending over approximately 12 years. Dr. Josef Miller has been the principal investigator for this period, with Dr. Ben Clopton serving as principal investigator during the final two months. This research has been conducted at the Department of Otolaryngology, University of Washington School of Medicine. Dr. Miller accepted the Directorship of the Kresge Hearing Research Institute, Department of Otorhinolaryngology, University of Michigan School of Medicine, as of 1 March 1984, and Drs. Clopton and Bryan Pfingst, co-investigators on the ONR contract, will join him at the University of Michigan 1 May 1984.

Inquiries regarding this work should be directed to:

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\*The very constructive guidance and organization of Dr. Frank Hemple of the Office of Naval Research has greatly facilitated this research.

## II. Final Progress Report

The primary goal of this program of research has been to evaluate the effects of middle ear pressure changes on hearing in humans. This research was initiated with the aim of determining the influence of maintaining static middle ear pressure on hearing function and describing the mechanisms that underlie these changes. The project was broadened to include an analysis of the mechanisms that underlie trauma to the inner ear caused by phasic changes in middle ear pressure, with values up to and including those that cause barotrauma in humans. Finally, the program was extended to incorporate an investigation of the interactive effects of noise and middle ear pressure on auditory function. This last feature of our program developed on the basis of a concern for the underwater and hyperbaric environments in which transtympanic pressure changes are frequently generated, i.e., many of these environments are quite noisy.

Our work in this area, on these three major questions, has been motivated by the need to: (1) understand the way in which pressure and noise may affect human communication and the mechanisms that underlie these effects, and (2) detect the presence of abnormal or subnormal middle ear function which may be either of clinical significance or predict susceptibility to damage.

Our strategy during the first seven years of this contract was to use a multidisciplinary approach to define the effects of these agents on



hearing and analyze the underlying physiological and anatomical mechanisms associated with each. This strategy dictated the use of animal models. During the last five years, we have attempted to extend aspects of this work to observations in humans. The aspects examined were those defined on the basis of our work with animals as representing selected critical variables. The aim was to evaluate the generality of our basic findings to humans.

An interesting and promising aspect of this project recently was the evaluation of the laser Doppler probe as a means for determining blood flow under a number of experimental conditions relevant to middle ear pressure and related parameters. This technique appears promising (see Miller, Marks, and Goodwin, 1983; Goodwin et al., 1984, manuscript in Appendix), and is being pursued beyond this project.

The progress on this project and the total program of research has been well-documented in publications and presentations. Major publications in the literature or submitted which have resulted from ONR support of this program number 42 at present. Numerous presentations at scientific meetings have also reported findings from this research. Publications, manuscripts, and presentations are listed in Section III of this report.

A major review article is in preparation by Dr. Miller. This work will summarize research findings in the literature bearing on middle ear pressure as well as the findings from this research program. It will derive implications of this work for normal auditory function in humans

as well as for otic pathologies related to pressure, noise exposure, and related potential insults to hearing function. This critical review will related to pressure, noise exposure, and related potential insults to hearing function. This critical review will attempt to integrate disparate views of middle ear function under parametric variation of middle ear pressure and propose directions for future research. In light of the extensive documentation of this research to date, a detailed description of the progress and implications of this research will be deferred for the upcoming review article.

## IV. Publications and Presentations Resulting from ONR Contract

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\* Major Publication.

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\* Major publication.

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\*Major Publication

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\*Major Publication



TITLE PAGE

Title:

The Laser Doppler: A Non-Invasive  
Measure of Cochlear Blood Flow

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ABSTRACT

The present investigation demonstrates the utility of the laser Doppler flowmeter to provide a measure of cochlear blood flow dynamics. Cochlear and cutaneous blood flow were compared with arterial blood pressure during and following exposure to Angiotensin II, 5% carbon monoxide, 100% oxygen, mannitol, and saline. The observations indicate that: 1) cochlear blood flow generally parallels cutaneous blood flow; however, 2) when cutaneous beds vasoconstrict (e.g., AII, alpha-agonists), cochlear blood flow parallels blood pressure; and, 3) under the influence of agents that affect peripheral and central circulation (5% CO, 100% O<sub>2</sub>), cochlear blood flow may dissociate from cutaneous blood flow and blood pressure. The implications of these findings are discussed in terms of local control mechanisms that may be involved in the inner ear vasculature.

## INTRODUCTION

Many cochlear pathologies have been attributed to vascular insufficiencies; however, no technique has been available to adequately assess cochlear blood flow dynamics. Techniques proposed for studies of vascular characteristics of the inner ear have included: 1) histological examination of temporal bone vascular beds (e.g., Hawkins, 1971; Axelsson & Vertes, 1982; Vertes & Axelsson, 1979; Johnsson, 1972); 2) microsphere studies (Angelborg et al., 1977; Hultcrantz et al., 1982; Larsen et al., 1982; Prazma & Rogers, 1982); 3) direct visualization of flow in selected cochlear vessels (Perlman & Kimura, 1955; Lawrence & Clapper, 1973); 4) impedance plethysmography (Suga & Snow, 1969), 5) ultrasonic Doppler (Krause et al., 1982), and 6) electrophysiologic measures of cochlear activity which may be related to blood flow (Maass, 1981; Prazma, 1981; Nuttall et al., 1980). In general, these techniques produce static (#1,2) or indirect (#1,4,5) measures of cochlear blood flow; they are either invasive (#3,4,5) or are contingent on the death of the subject (#1,2); some are difficult to quantify (#3,4) or provide a very restricted area of study (#3) or provide a large undefined area of study (#4,5); and histological and electrophysiological measures may be only circumstantially related to flow. Such studies have contributed to hypotheses regarding the role of compromised inner ear blood flow in sudden deafness (Seigel, 1973), noise exposure (Axelsson & Vertes, 1982; Vertes et al., 1979; Prazma et al., 1983; Nuttall et al., 1980), Meniere's disease

(DeVincetis et al., 1964; Prazma, 1981), and certain congenital pathologies (Johnsson, 1972; Kikuchi & Hilding, 1967).

Recently, Miller et al. have reported findings using a laser Doppler flowmeter to monitor cochlear and cutaneous blood flow dynamics (Miller et al., 1983; Miller et al., in press). Systematic changes were found with rebreathing, CO<sub>2</sub>, administration of an alpha-agonist and an antagonist, and terminal asphyxia. Observed cochlear flow changes typically paralleled skin flow, but showed some variation as might be expected in a system with a vascular supply common with the central nervous system.

In this paper we examined the effects of two types of agents. The first type consisted of agents known to have profound selective effects on different vascular beds. These agents included 1) Angiotensin II (AII), which is a potent peripheral vasoconstrictor that elevates arterial blood pressure, and 2) Carbon monoxide (CO), which increases cerebral blood flow and is associated with a decrease in arterial pressure (Koehler et al., 1982). If the vessels of the inner ear are not locally regulated (i.e., their caliber is fixed), then blood flow through those vessels should be directly dependent on systemic blood pressure. If, however, the inner ear vessels are locally regulated, then cochlear blood flow could be independent of arterial blood pressure under certain conditions. AII and CO were selected because they are known to produce dissociation between arterial blood pressure and flow in different vascular beds.

The second group of agents was selected because they have been used therapeutically for treating inner ear disorders believed to be of vascular etiology. The first of these was mannitol, which is an osmotic diuretic (Goodman & Gilman, 1975) that has been used to decrease cerebrospinal fluid pressure in shock and trauma. It has been suggested that mannitol increases cochlear blood flow by increasing the plasma volume (Larsen, 1982). The second agent in this group was oxygen, which has been utilized in clinical trials for the treatment of temporary threshold shift (Joglekar et al., 1977). Oxygen also serves as a control for the respiratory status of the subject. While we would not expect change in cochlear blood flow in a properly ventilated animal, a change might occur if the animal were hypoxic prior to oxygen administration.

#### MATERIALS AND METHODS

Twelve adult Hartley guinea pigs with normal Preyer reflexes and middle ears were used in this study. Each subject was anesthetized with 30.0 mg of ketamine hydrochloride and 4.0 mg of xylazine and maintained with a 20:1 mix of ketamine:xylazine. Core temperature was maintained with a heating pad. The head was rigidly fixed during measurement via a head post, which was secured to the cranium with self-tapping screws and dental acrylic. The trachea and a femoral artery were cannulated to allow administration of vasoeffector gases and drugs. Blood pressure was monitored through the femoral arterial catheter by a strain gauge (Stratham model P23Db). The bulla was opened by a ventral approach

exposing the first and second turns of the cochlea. Lateral wall mucosa was gently removed with a cotton pledgette to eliminate mucosal vasculature and to permit approximation of the measurement probe (see below) to the bony surface of the lateral wall of the basal turn. The probe surface was placed normal to the curvature of the promontory centered over the stria vasculature (Fig. 1). A second measurement probe (see below) was used to monitor skin flow from a shaved area on the flank.

Two laser Doppler systems were used in this study: a Medpacific (LD-5000) and a Perimed (Periflux). In both systems, a helium-neon laser produces a monochromatic light source (632.8 m) which is reflected well by red blood cells. Quartz optical fibers conduct light emitted by the laser to the measurement probe. Light emitted by the probe is either absorbed or reflected by the medium it strikes. Light reflected by stationary media has the same frequency as the emitted light, while light reflected by moving media (e.g. red blood cells) is shifted in frequency according to the Doppler principle. Reflected shifted and non-shifted light heterodyne at the surface of the measurement probe. In the LD-5000, this heterodyned signal is transmitted by a single sensor fiber to a photodiode. This signal is processed to yield a voltage which is proportional to the product of the number of particles within the measurement volume ( $1.0-1.5 \text{ mm}^2$ ) and the velocity of those particles, i.e., blood flux (Nilsson et al., 1980). When used to monitor skin perfusion, the laser Doppler output was found to be linearly proportional to blood flow as confirmed by other blood flow measurement techniques,

including xenon clearance, microspheres, and plethysmography (Bonner et al., 1981; Halloway, in press).

In the Perimed system (Periflux), the probe contains two parallel sensor systems with a single emitting source. The heterodyned signal from this system is transmitted by two sensor fibers and the output is processed to yield a differential measure, which should be less sensitive to "noise," such as gross movement artifacts. We have compared the outputs of the two systems and have found them to be equivalent in our rigidly fixed preparations. Typically, we monitored cochlear blood flow with the Perimed device (2.25 mm needle probe) and skin flow with the MedPacific flowmeter with an acrylic skin probe. Figure 1 is a schematic of the relative proportions and positioning of the Perimed needle probe. The output voltages of these devices and blood pressure were recorded on a Sanborn polygraph (model 850). For further information regarding the development and theory of the laser Doppler flowmeter, see Bonner et al. (1981), Nilsson et al. (1980), and Miller et al. (1983).

The agents examined in this study (Table I) each have known vascular effects. Each of the gases was presented after a 30-sec or more baseline monitor period. The gases were administered via the tracheal cannula: O<sub>2</sub> for 1.0 min, O<sub>2</sub> and 5% CO in 95% air for 0.5 min. Care was taken to minimize positive end expiratory pressure (PEEP). One and one-half cc of 0.9% isotonic saline (pH 4.5-7.0), 1.5 cc of 20% mannitol (Osmitol pH 5.5), and 0.5 cc of 0.9% saline containing 100 pM/kg of Angiotensin II (AII) were injected intra-arterially as a bolus after prewarming to body

temperature. The mode of delivery and number of observations for each agent is shown in Table I.

TABLE I

PROTOCOL		
<u>Vasoeffector</u>	<u>Mode of Exposure</u>	<u>Number</u>
O <sub>2</sub> gas	Tracheal Cannula	6
5% CO gas	Tracheal Cannula	2
Angiotensin II	Femoral Artery Catheter	6
Mannitol/Saline	Femoral Artery Catheter	4
Subject Total* =		12

\*Multiple substances were used on most guinea pigs.

While the laser Doppler flowmeter provides a linear real-time measure of blood flow, the output is relative and not quantifiable at present in physical units of flow. Therefore, the blood flow data in this paper are presented as a percent of the average baseline change (% ABL). Each trace was digitized in 6-second sample periods which were determined to provide adequate temporal resolution for the agents examined. These scores were then converted to % ABL, entered into a DEC-10 computer, and graphed versus time with a conventional graphics program.



## RESULTS

TABLE II

## Results

Agent	<u>Early Effects</u>			<u>Late Effects</u>			<u>Recovery</u>		
	Skin	BP	Cochlea	Skin	BP	Cochlea	Skin	BP	Cochlea
AI1	↓	↑	↑	↓	↑	↓	Y	Y	Y
CO	∅	↓	↑	∅	↓	↑	Y	Y	N
O <sub>2</sub>	∅	↑	∅	∅	∅	↓	Y	Y	Y
Mannitol	↑	↑	↑	↑	↑	↑	slow	Y	Y

Table II summarizes the graphic data presented in this paper. "Down arrows" signify a decrease in that measure, "up arrows" signify an increase, "∅'s" signify no change, "Y" indicates yes and "N", no.

Figure 2 portrays the effects of an arterial injection of 100  $\mu\text{M/kg}$  of AI1 (arrow). Blood pressure rose rapidly from a mean arterial pressure of 67 cm H<sub>2</sub>O to 118 cm H<sub>2</sub>O within 0.9 min ( $\tau = 0.4$  min), it then returned in a steady manner over the next 2.5 min to baseline. Skin blood flow exhibited an immediate, small, transient increase followed by a rapid drop to a minimum of 35% ABL at 0.9 min following AI1 injection ( $\tau = 0.2$  min). Skin flow then rose steadily to 80% ABL at the end of the observation period (3.5 min after the AI1 injection). Cochlear blood flow first rose at 0.2 min post injection, attaining a value of 150% ABL at 0.7 min post injection ( $\tau = 0.4$  min). It then returned steadily to the

baseline value at 1.7 min post injection and demonstrated some further decrease to 90% ABL at the end of the observation period.

Figure 3 represents the effects of 0.5 min breathing 5% carbon monoxide in 95% air (between arrows). Diastolic blood pressure decreased from 59 cm H<sub>2</sub>O to 41 cm H<sub>2</sub>O during the exposure period and partially recovered to 44 cm H<sub>2</sub>O at 4 min post exposure. Skin flow decreased to 85% ABL through the exposure period; it then demonstrated considerable, atypical oscillations, but remained at about 85% ABL throughout the 4-min observation period. Cochlear blood flow dropped to 90% ABL through the exposure period, rose to 155% ABL at 1.9 min following exposure, and recovered partially to 140% ABL at 4 min post exposure. Recovery was not complete within the 15-min period post exposure.

Figure 4 represents the effects of 1 min breathing 100% O<sub>2</sub> (between arrows). Diastolic blood pressure rose from 63 cm H<sub>2</sub>O to 72 cm H<sub>2</sub>O through the 1 min of O<sub>2</sub> exposure. Blood pressure then slowly decreased approximately to baseline (60 cm H<sub>2</sub>O) at 2 min after termination of 100% O<sub>2</sub> exposure. Cutaneous and cochlear blood flow exhibited increased variability during 1.0 min exposure to oxygen with no clear net change in blood flow. Following termination of O<sub>2</sub>, cutaneous flow stabilized at 100% ABL while cochlear flow decreased to 76% ABL 0.8 min after 100% O<sub>2</sub> exposure, then slowly recovered to baseline.

Figure 5 shows the typical effects of mannitol in comparison to normal saline. The arrows on the graph indicate the time at which each injection was initiated. Skin blood flow increased a maximum of 18% 30 sec after the injection of 1.5 cc of 0.9% saline (dotted lines). Skin

blood flow then began to decline from a 10% mean increase to 5% mean increase at the end of the monitoring period (14 minutes post injection). Skin blood flow typically returned to baseline within 20 min. The saline injection caused cochlear blood flow to increase a maximum of 20% within 30 sec following administration. Cochlear flow returned to baseline within 3 min post injection and fell to 85% ABL 10.6 min after the injection. Cochlear flow recovered to baseline within 13 min post injection. Blood pressure increased only nominally and recovered to baseline rapidly.

In response to injection of 1.5 cc of 20% mannitol (solid line), blood pressure increased from 40 cm H<sub>2</sub>O to a maximum of 56 cm H<sub>2</sub>O (40% increase) within 3.75 min postinjection, and recovered to 5% above baseline at the end of the recording period. Blood pressure typically recovered within 20 min post injection. Skin blood flow increased to a maximum of 70% above baseline within 1 min post injection and remained elevated throughout the measuring period. Total recovery usually took longer than 30-45 min. Cochlear blood flow increased to a maximum of 60% within 45 sec post injection and recovered to baseline within 9.5 min post injection.

#### DISCUSSION

The laser Doppler flowmeter has been shown to measure blood flux. This has been demonstrated and confirmed independently by Bonner et al.

(1981) and Nilsson et al. (1980) in both theoretical and empirical studies. We have completed two studies of cochlear blood flow using the laser Doppler flow meter (Miller et al., 1983; Miller et al., in press) which indicate that it provides a valid measure of cochlear flow. Given the anatomy of guinea pig cochlear vasculature and the measuring depth of the laser Doppler system (1.0-1.5 mm in skin), it is reasonable to conclude that we are monitoring blood flow in stria vascularis, the vessels of the vestibular membrane, and the spiral ligament vessels with perhaps a contribution from the preterminal radiating arterioles and initial segments of the collecting vessels. While the device does not provide an output quantifiable in number of RBC/volume of tissue/time, it does provide a linear and relative measure of blood flow; and since it is a "real time" measure, it permits a direct evaluation of the dynamics of blood flow. It is difficult to conceive of any changes in the temporal bone other than blood flow in the inner ear that could produce the effects observed.

It has been previously shown (Miller et al., 1983) that skin and cochlear blood flow often parallel each other. This has been demonstrated by short periods of rebreathing (Miller et al., 1983). The results of the AII experiment indicate that in response to some agents, skin and cochlear flow dissociate. Under most conditions, this dissociation was believed to be indicative of cochlear flow responding "passively" to changes in blood pressure, as in Fig. 2. This is consistent with the known effects of AII on skin blood flow and arterial pressure.

Five-percent carbon monoxide and 100% oxygen caused blood pressure and cochlear flow to dissociate (Figs. 3 and 4). While the short exposure to 100% O<sub>2</sub> would seem insufficient to cause any toxic effects, there does appear to be an "off-effect" in which cochlear flow drops while blood pressure is maintained at elevated levels (Fig. 3). With exposure to CO, this dissociation between each flow and blood pressure is clear. Cochlear blood flow rises significantly while blood pressure is depressed and skin is unaffected (Fig. 4). While we are unable to propose definitive mechanisms underlying this effect, it is clear that some local control mechanisms are involved in this response. Keohler et al. (1982) have shown that CO increases CNS blood flow, probably via a hypoxic response. Our findings, therefore, suggest that similarities exist in the control mechanisms of CNS and cochlear blood flow. We are currently comparing the nature of these responses in hopes of determining if the control mechanisms are quantitatively and temporally correlated.

Given the plasma expanding characteristics of mannitol, we predicted increase in blood flow to the cochlea primarily reflecting the increase in systemic blood pressure (Larsen, 1982). Indeed, this was observed. Cochlear and cutaneous blood flow and arterial blood pressure increased significantly with mannitol injections; however, the time courses of these increases suggest that some alternative mechanisms are involved. If the changes in cochlear and cutaneous blood flow are due to the change in blood pressure, then the rise and fall in the blood flow would be temporally correlated with the blood pressure changes or at least would succeed the blood pressure changes. However, the cochlear and cutaneous

## The Laser Doppler

blood flow changes precede the pressure changes. Moreover, the onset of the blood flow increases appear to be temporally correlated, while the onset of the decreases are correlated neither to each other nor to blood pressure. This suggests that: 1) cochlear and cutaneous blood flow changes associated with mannitol injection are not directly caused by blood pressure changes, and 2) the mechanism(s) underlying the blood changes are different in the cochlea than in the skin and are not temporally correlated.

These observations support the conclusion of previous papers that the laser Doppler flowmeter provides a useful measure of cochlear blood flow (Miller, 1983; Miller, in press). The results of this paper suggest some basic characteristics of the control of cochlear vasculature: under normal conditions, cochlear blood flow parallels cutaneous blood flow. However, when skin is affected by vasoactive drugs [i.e. Angiotensin alpha-agonist (Miller et al., in press)], cochlear flow will tend to follow blood pressure. And finally, there are conditions during which cochlear blood flow responds in a manner unlike both skin blood flow and femoral artery blood pressure. Presumably these changes reflect local control mechanisms of blood flow within the cochlea. It is premature to speculate on the form of the mechanisms underlying the local control. We are currently pursuing the hypothesis that these local control mechanisms are common with those of the CNS and that cochlear blood flow is correlated with cerebral blood flow.

#### ACKNOWLEDGEMENTS

This work was supported by the Office of Naval Research (ONR) grant number N00014-75-C-0463 MDD P00009. We would like to thank Ms. Marcy Brooks-McAuliffe and Ms. Trudy Schleicher for their assistance in preparation of this manuscript.

## FIGURE LEGENDS

## Figure 1 The Laser Doppler Needle Probe.

This is a schematic of the laser Doppler needle probe of the Perimed system. The relative positioning of the emitting and sensor probes are seen in end view (A) and relative to the basal turn of a guinea pig cochlea (B).

## Figure 2 Angiotensin II.

100 pm/kg of Angiotensin II (AII) was injected intra-arterially (arrow). The responses of cochlear blood flow (—) and skin blood flow (---) are depicted in the upper figure. The bottom figure depicts the response of diastolic blood pressure at the femoral artery.  $\tau$  = time to  $[(1 - 1/e) \times \text{maximum change}]$ .

## Figure 3 Carbon Monoxide.

5% carbon monoxide in 95% air was introduced intratracheally for 30 sec beginning with the first arrow and ending with the second arrow. Positive End Expirating Pressure (PEEP) was avoided. The responses of cochlear blood flow (—) and skin blood flow (---) are depicted in the upper figure and the response of blood pressure measured in the femoral artery is shown in the lower figure.

## Figure 4 100% Oxygen.

100% oxygen was introduced intratracheally for 1.0 min (between arrows). The responses of cochlear (—) and skin (---) blood



flow are in the upper figure and the response of blood pressure measure at the femoral artery is shown in the lower figure.

Figure 5 Mannitol and Saline.

The responses of cochlear blood flow (upper figure), blood pressure (middle figure) and skin blood flow (lower figure) to mannitol (—) and 0.9% saline (---) are depicted. For both mannitol and saline, the injections required 30 sec and were initiated at the arrows.

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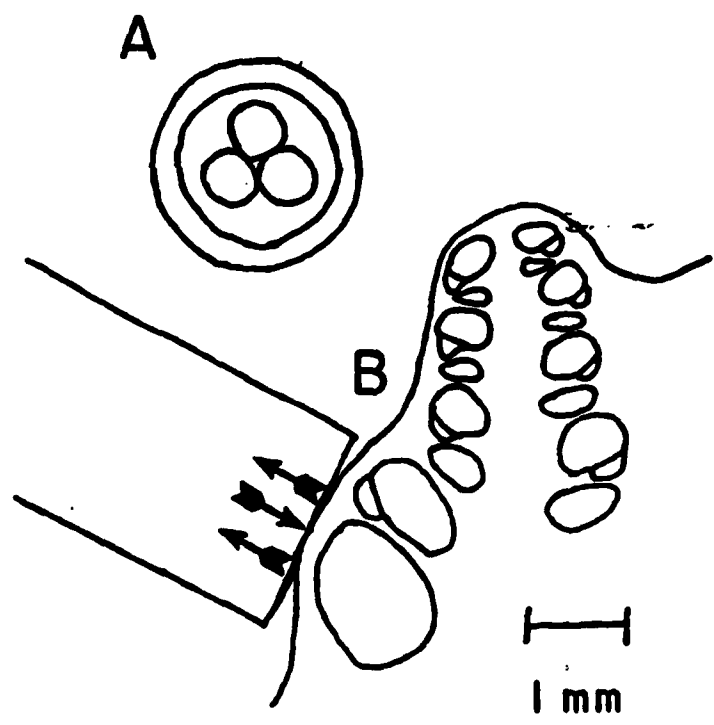
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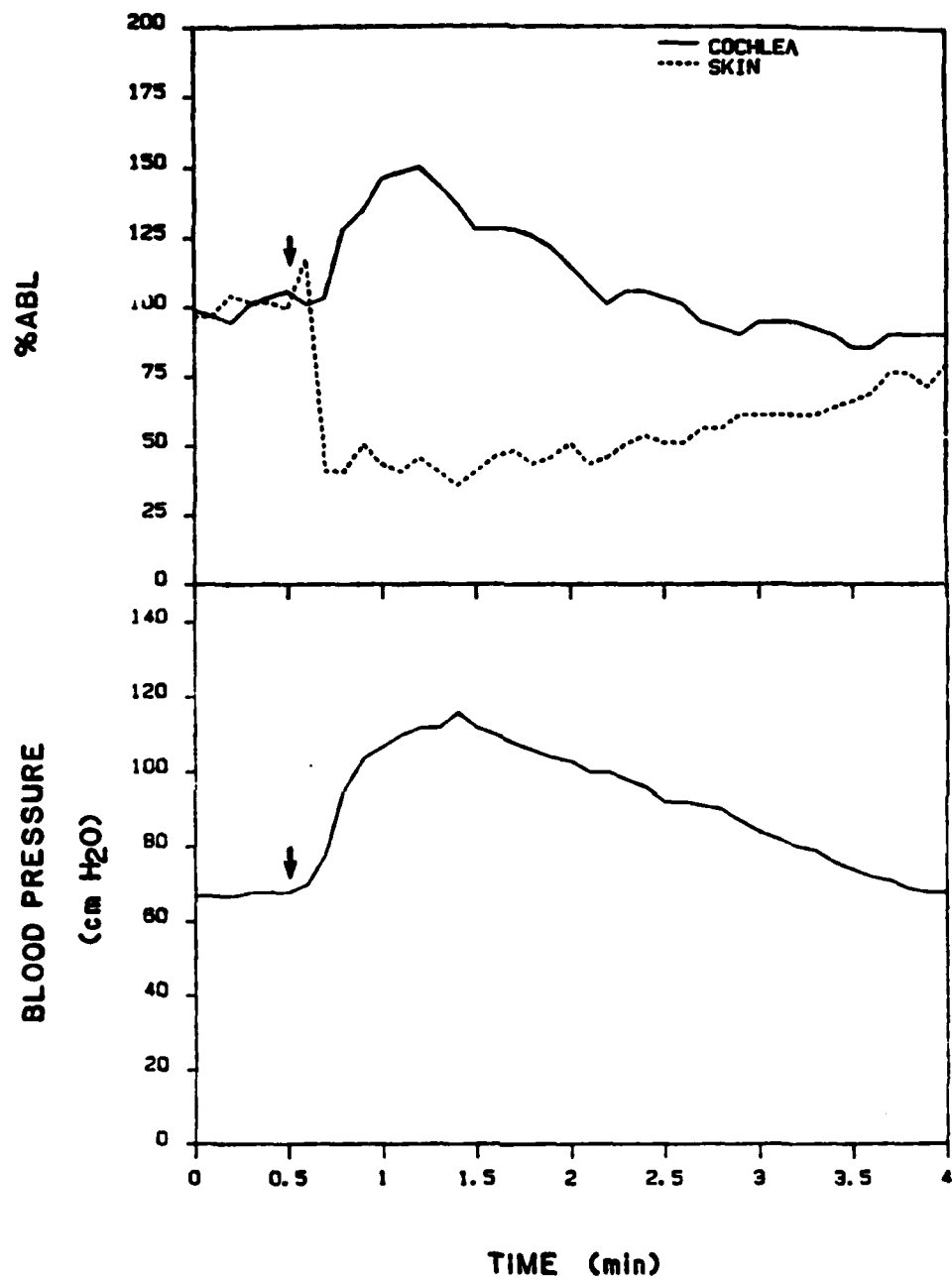
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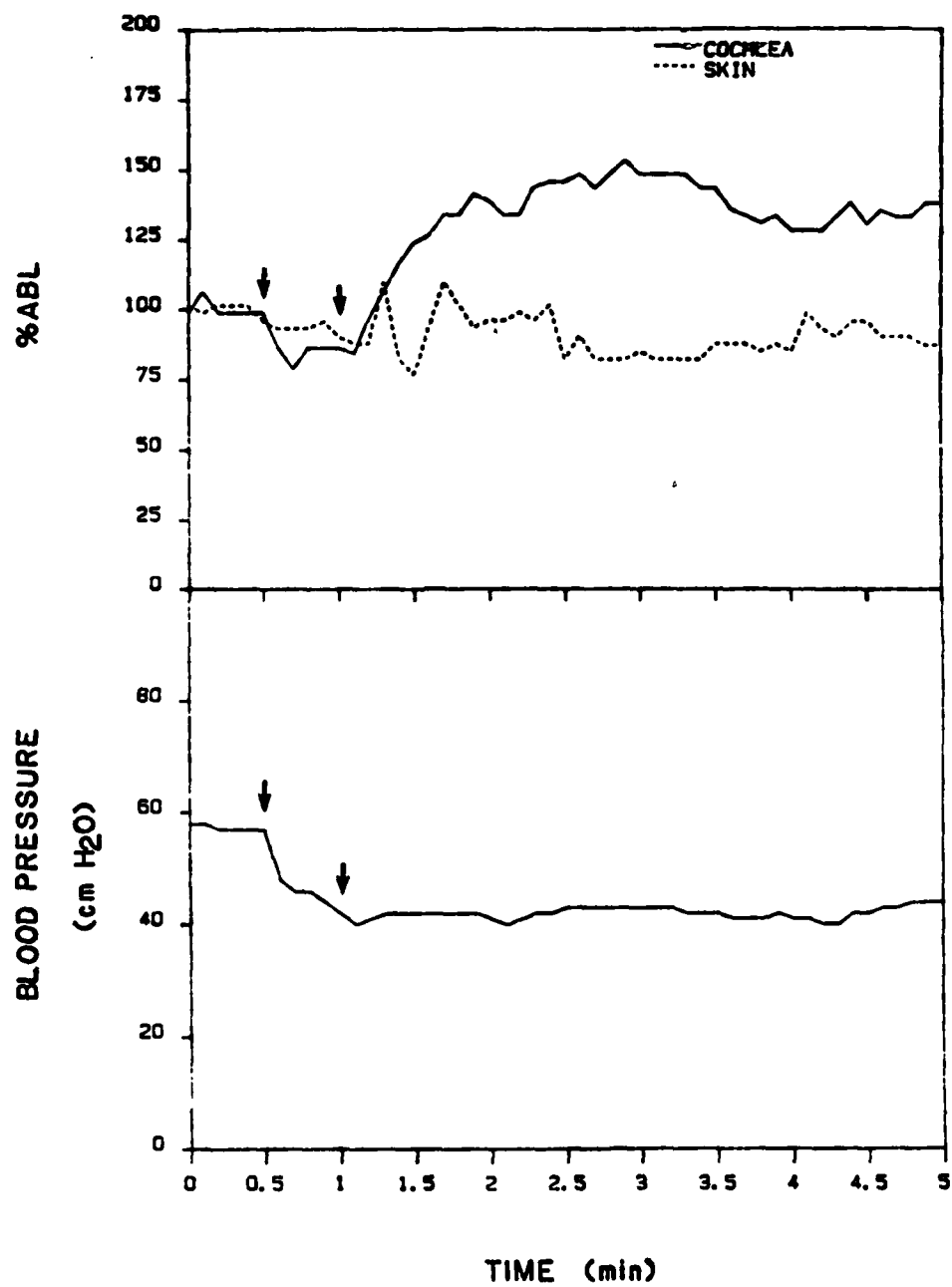
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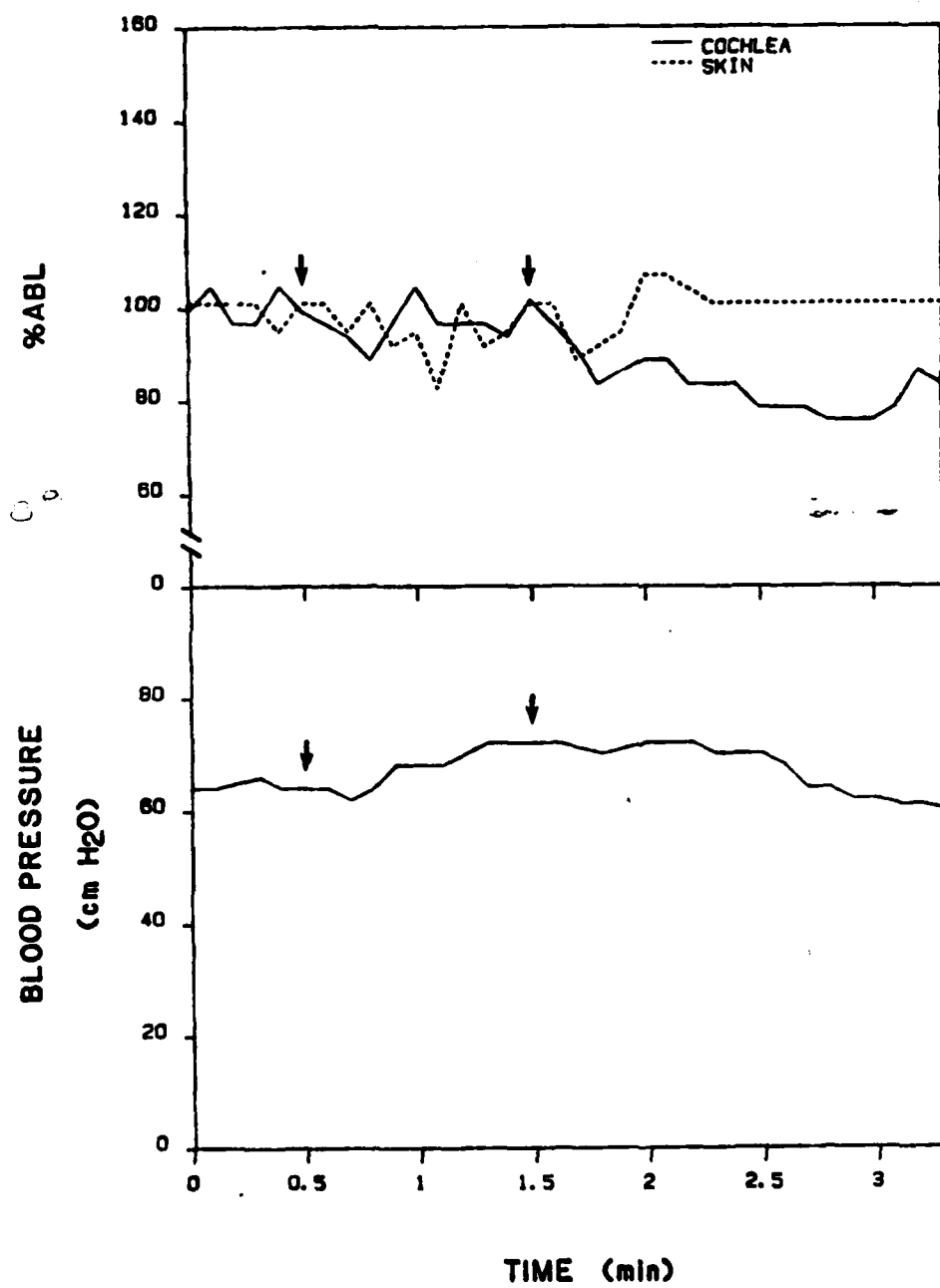


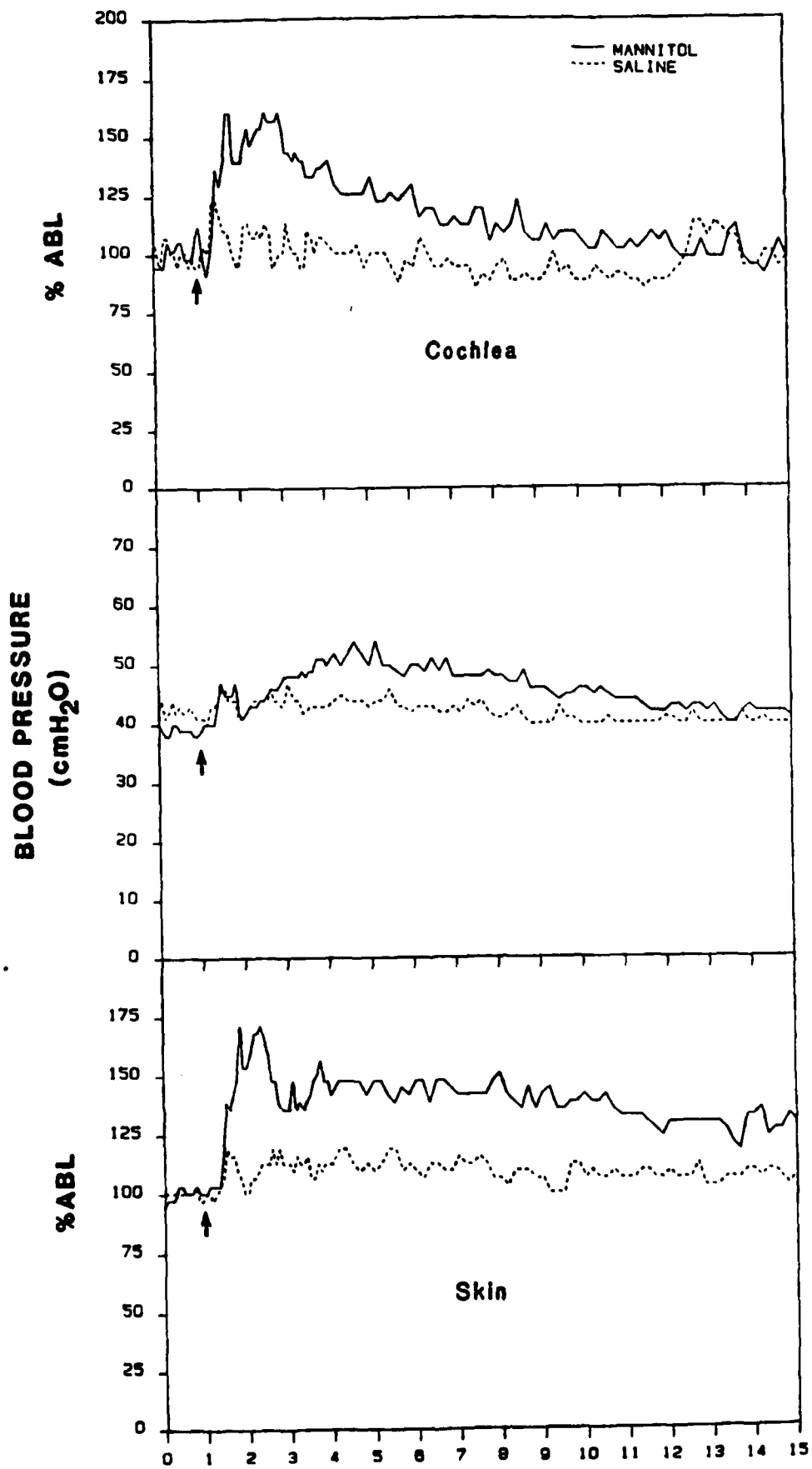


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