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Perspectives on limb-vascular heterogeneity: Implications for human aging, sex, and exercise.

Thesis for the degree dr.philos

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Norwegian University of Science and Technology
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Sammendrag:

TITTEL: Perspektiver på vaskulære forskjeller i armer og bein: Implikasjoner for menneskers aldring, kjønn og trening.

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Mye forskning som vurderer blodstrøm i human skjelettmuskel er blitt gjennomført, som reaktiv hyperemi og muskelmetabolisme i isolerte muskler, men det er et relativt fåtall studier som har undersøkt vaskulære og metabolske forskjeller i armer og bein både i hvile og under metabolsk utfordrende perioder som trening og avstenging av blodstrøm med trykkmansjetter. Imidlertid har nylig noen spennende og klinisk signifikante forskjeller mellom armer og bein blitt tydeliggjort både hos friske og sykdomsrammede, og hos de siste synes det som om beina har en større grad av vaskulær dysfunksjon. For å forstå bedre vaskulær kontroll og patologi (e.g. aldring og perifer arteriell sykdom/ intermittent claudication) som gir utslag i større grad av vaskulære forskjeller, gjennomførte vi en serie protokoller som var designet for å evaluere skjelettmusklenes metabolske og vaskulære reguleringsmekanismer og implikasjonene for forskjellige grupper av befolkningen (i.e. alder og kjønn).

Flere nye metodologiske teknikker (ultralyd/doppler, nukleær magnetisk resonans (NMR) og elektron paramagnetisk resonans (EPR) ble brukt for å måle fysiologiske variabler (blodstrøm, reaktiv hyperemi, oxidativ metabolisme, bioenergi og produksjon av frie radikaler) ved bruk av eksperimentelle protokoller som inkluderte isolert dynamisk arbeid, kuldestimulert konstriksjon, inntak av anti-oksidanter og bruk av trykkmansjetter for å indusere oksygenmangel. Totalt 140 friske forsøkspersoner (122 unge (23±2 år) forsøkspersoner (105 mannlige og 17 kvinnelige) og 18 eldre (72±2 år) forsøkspersoner (16 mannlige og 2 kvinnelige)) deltok i studiene. Avhengig av eksperimentoppsett og måleteknikker ble målingene gjort i arm (brakiale a.) og bein (enten de femorale arteriene eller poplietal a.). Disse studiene ga følgende resultater: 1) det er en arbeidsindusert avhengighet av pro oxidant stimulert vasodilatasjon, som viser en viktig og positiv vaskulær rolle for frie radikaler, 2) vasokonstriksjon mediert via sympaticus uttrykkes likt både i armer og bein i hvile både for trente og utrente forsøkspersoner, men med forskjellig utvikling av vasokonstriksjon under akutt arbeid både med hensyn på arm- og beinforskjeller og treningsstatus, 3) leggmusklene i en ung frisk gruppe forsøkspersoner viste en svekket reperfusjon respons, mens arterie blodstrøms-mediert dilatasjons data paradoksalt viser at bein har større vaskulær reaktivitet enn arm, 4) aldring har en arm og beinspesifikk effekt på vaskulær struktur, reaktiv hyperemi og arbeidsindusert blodstrøm, og 5) uavhengig av kjønn er reaktiv hyperemi større i beina og kvinner har den samme vaskulære funksjon i armer, men er svekket i beina.

Samlet sett ser det ut til at arm- og beinforskjeller eksisterer, og i forskjellig grad i forskjellige deler av befolkningen. Disse studiene har belyst flere underliggende mekanismer som definerer forskjeller i vaskularitet, som alle er viktige for å forstå blodstrøm i skjelettmuskel og vaskulære kontrollmekanismer ikke bare i den friske delen av befolkningen, men også i sykdomsgrupper som synes å vise arm- og beinspesifikke vaskulære funksjonsproblemer.

Summary:

TITLE: **Perspectives on Limb-Vascular Heterogeneity: Implications for Human Aging, Sex, and Exercise**

AUTHOR: **Steven K. Nishiyama**

Considerable research addressing human skeletal muscle blood flow, vascular reactivity, and muscle metabolism has been performed in isolated limbs, but there is a relative paucity of studies that have assessed limb-specific vascular and metabolic differences both at rest and during metabolically challenging periods such as exercise and cuff-ischemia. However, recently some intriguing and clinically significant between-limb heterogeneities have become apparent in both health and disease, in the latter the lower extremities exhibiting the higher degree of vascular dysfunction. To better understand local vascular control and the multiple pathologies (e.g. aging and peripheral artery disease) that exhibit limb-specific tendencies, we conducted a series of protocols designed to systematically evaluate vascular limb heterogeneities with respect to skeletal muscle metabolic and vascular regulatory mechanisms and the implications for differing populations (i.e. age, sex).

Multiple novel methodological techniques (Ultrasound Doppler, Nuclear Magnetic Resonance (NMR), and Electron Paramagnetic Resonance (EPR)) were utilized to assess physiological variables (blood flow, vascular reactivity, oxidative metabolism, bioenergetics, and free radical generation, respectively) during experimental protocols which included isolated dynamic exercise, cold-pressor stimulation, anti-oxidant administration, and ischemic cuff-occlusion. A total of 140 healthy subjects (122 young (23 ± 2 yrs) subjects (105 males and 17 young females) and 18 old (72 ± 2 yrs) subjects (16 males and 2 females)) participated in these studies. Dependent on experimental modality and technique, measurements were made in the arm (brachial artery) and leg (either the femoral arteries (common, deep, and superficial) or popliteal artery). These studies revealed the following results: 1) There is an exercise-induced reliance upon pro-oxidant stimulated vasodilation thereby revealing an important and positive vascular role for free radicals, 2) Sympathetically mediated vasoconstriction is expressed equally and globally at rest in both sedentary and trained individuals, with a differential pattern of vasoconstriction during acute exercise according to limb and exercise training status, 3) The lower legs in a young healthy group of human subjects exhibit an attenuated ischemic reperfusion response, while conduit artery flow-mediated dilation data paradoxically reveal that the lower legs have greater vascular reactivity that the arm, 4) Aging has a limb-specific effect on vascular structure, vascular reactivity, and exercise-induced blood flow, and 5) Regardless of sex, vascular reactivity is greater in the legs and women have similar vascular function in the upper extremities, but this is attenuated in the lower extremities.

Collectively, inherent limb differences appear to exist, and to different extents in varied populations. These studies have elucidated several underlying mechanisms defining vascular heterogeneities, all of which are important for understanding skeletal muscle blood flow and vascular control mechanisms in not only a healthy population, but also in diseased populations that tend to exhibit limb-specific vascular dysfunction.

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LIST OF PAPERS

This thesis consists of the following publications, which will be referred to by their roman numerals.

I. Richardson R.S., A.J. Donato, A. Uberoi, D.W. Wray, L. Lawrenson, S.K. Nishiyama, and D.M. Bailey. Exercise-induced brachial artery vasodilation: The role of free radicals.
Am J Physiol Heart Circ Physiol. 2007 Mar; 292(3):H1516-22.

II. Wray, D.W., A.J. Donato, S.K. Nishiyama, and R.S. Richardson. Differential sympathetic control of limb blood flow at rest and during exercise in cyclists and sedentary adults.
J Appl Physiol. 2007 Feb; 102(2):704-12.

III. Nishiyama, S.K., D.W. Wray, K. Berkstresser, M. Ramaswamy, and R.S. Richardson. Limb-specific differences in flow-mediated dilation: The role of shear rate.
J Appl Physiol. 2007 Sep; 103(3):843-51.

IV. Nishiyama, S.K., D.W. Wray, A. Monnet, P.G. Carlier, J. Hoff, and R.S. Richardson. Control of skeletal muscle blood flow: Are all limbs created equal?
Submitted for review

V. Donato AJ, A. Uberoi, D.W. Wray, S. Nishiyama, L. Lawrenson, and R.S. Richardson. Differential effects of aging on limb blood flow in humans.
Am J Physiol Heart Circ Physiol. 2006 Jan; 290(1):H272-8.

VI. Nishiyama, S.K., D.W. Wray, and R.S. Richardson. Aging affects vascular structure and function in a limb-specific manner
Submitted for review

VII. Nishiyama, S.K., D.W. Wray, and R.S. Richardson. Sex and limb-specific ischemic reperfusion and vascular reactivity
Submitted for review

ABREVIATIONS

ANOVA	Analysis of Variance
ASL	Arterial Spin Labeling
ATP	Adenosine Tri-Phosphate
AU	Arbitrary Units
AUC	Area Under Curve
BA	Brachial Artery
Ca^{++}	Calcium Ion
CFA	Common Femoral Artery
CNS	Central Nervous System
CPT	Cold-Pressor Test
deoxy-Mb	deoxy-Myoglobin
DFA	Deep Femoral Artery
ECG	Electrocardiogram
EDHF	Endothelial-Derived Hyperpolarizing Factor
eNOS	Endothelial Nitric Oxide Synthase
EPR	Electron Paramagnetic Resonance
FID	Free Induction Decay
FMD	Flow-Mediated Vasodilation
H_2O_2	Hydrogen Peroxide
IMT	Intima-Media Thickness
mm HG	millimeters of Mercury
MVC	Maximum Voluntary Contraction
N_2	Molecular Nitrogen
NADH	Nicotinamide Adenine Dinucleotide
NMR	Nuclear Magnetic Resonance
NO	Nitric Oxide
O_2	Molecular Oxygen
O_2^-	Superoxide Anion
$ONOO^-$	Peroxynitrite
PA	Popliteal Artery
PBN	α-phenyl-tert-butylnitrone
PCr	Phosphocreatine
PGI_2	Prostacyclin
P_i	Inorganic Phosphate
ppm	Parts Per Million
Q	Blood Flow
ROI	Region of Interest
SE	Standard Error
SFA	Superficial Femoral Artery
SNA	Sympathetic Nerve Activity
V_{mean}	Mean Blood Velocity
$\dot{V}o_{2max}$	Maximal Oxygen Consumption
WR_{max}	Maximal Voluntary Work Rate

INTRODUCTION

VASCULAR CONTROL MECHANISMS

Central and Local Mechanisms Governing Vascular Function and Muscle Blood Flow

The human vasculature is a complex, dynamic system which precisely regulates the delivery of blood to all regions of the body. Regulation of these vascular responses involves the coordination of various central and local mechanisms all of which exist and act to successfully match the supply of blood with the metabolic demand of various tissues under wide-ranging conditions (91, 107). Blood flow is principally dictated by the product of vessel diameter and blood velocity, thus, the degree of vascular tone as well as the impact of controlling blood velocity are key determinants of blood flow. Accordingly, central and local factors act together to vary 1) the degree of vascular smooth muscle "tone", which ultimately determines the diameter of the blood vessel, and 2) the arterial pulse pressure, which ultimately determines the velocity of the blood. The central control mechanisms consist primarily of neuronal and hormonal factors, and are responsible for regulating cardiac activity and regional vascular tone. As such, the central mechanisms are designed for the maintenance of systemic blood pressure and central cardiovascular homeostasis. Equally as important, vascular control is also regulated by local factors such as autocrine and paracrine substances, metabolic bi-products, and mechanical stimuli such as shear stress (80). In contrast to the central mechanisms, local vascular control mechanisms are designed to maintain site-specific vascular homeostasis.

Hormonal factors can influence vascular tone in skeletal muscle, but they appear not to be of foremost importance in vascular control, particularly during a dynamic challenge such as exercise. However, nervous regulation by the autonomic nervous system controls both the central (e.g. heart) and peripheral (e.g. vascular resistance and conductance) mediators of the circulation and is of paramount importance in acute vascular control (20,

50). The combination of signals from central motor systems and by peripheral sensors (e.g. baroreceptors, muscle chemosensors, and mechanoreceptors) being integrated by the central nervous system (CNS) provides a major feed-forward and feed-back system with a high degree of specificity (171). By altering efferent outflow of the sympathetic and parasympathetic system, CNS nervous activity subsequently influences heart rate, cardiac output, and vascular tone, and thus, blood flow.

Vascular function is also influenced by local mechanisms that specifically regulate vascular tone in a localized area. Two principal local mechanisms are the metabolic vasoactive milieu and vascular myogenic activity (37). The metabolic vasoactive milieu consists primarily of mediators from the vascular endothelium and muscle fibers (e.g. adenosine, nitric oxide (NO), oxidative stress), acting through pharmaco-mechanical coupling to promote vascular contraction or relaxation (107). Vascular smooth muscle is also controlled by an inherent constriction in response to stretch, normalizing changes in pressure across the vessel wall, the myogenic response (90).

Collectively, both central and local systems govern vasomotion through vasoconstrictor and vasodilator processes and thus regulate the circulation of blood in an elegant and dynamic fashion. However, details regarding this interaction between local metabolic and systemic vascular control mechanisms, as well as the limb-specific variation that occurs in healthy young and senescent populations are certainly not well understood.

Vascular Endothelial Function and Shear Stress

In 1980 Furchgott and Zawadzki discovered the role of the vascular endothelium as a modulator and initiator of vasomotion, forever changing the landscape of vascular biology (62). Previously characterized as simply a physical barrier between the blood and the vascular wall, the vascular endothelium is the monolayer of cells lining all of the blood vessels in the

body that responds to both chemical and physical stimuli and forms an important component of local vascular regulation and vascular health (204). In a non-diseased/ healthy state, the endothelium releases a balance of autocrine and paracrine substances that modulate vascular tone and permeability, as well as angiogenesis and inflammation (55). Endothelial function is therefore an essential component to vascular homeostasis and control. Conversely, endothelial dysfunction is associated with the disruption in this delicate balance, adopting a phenotype that facilitates inflammation, thrombosis, vasoconstriction, and atherosclerotic lesion formation (113). Furthermore, the present body of knowledge supports the notion that endothelial function has prognostic value for cardiovascular risk, indicating that endothelial dysfunction plays a significant role in the development and progression of vascular pathology (21, 204).

One of the most important stimuli for the release of endothelial-derived factors is blood flow-associated shear stress (144). The endothelial response to shear stress includes changes in ionic conductance and the production of vasoactive molecules. This is followed by continuing signaling cascades and transcription factor activation, protein synthesis, and finally structural changes to alleviate the elevated shear stress (33). Shear stress refers to the laminar frictional force exerted by the blood as it moves along the vessel wall and is represented by the equation: $\eta V/D$ (where η = blood viscosity, V= blood flow velocity and D = vessel diameter) (64). A shear stress stimulus under experimental conditions, typically an elevation in blood flow, is created by decreasing downstream vascular resistance so that flow through the feeding conduit artery is increased. A reduction in downstream vascular resistance can be achieved in several ways and the method employed determines the profile of the shear stress stimulus in the conduit artery. The technique predominantly used in eliciting this response was first described and employed by Celermajer *et al.* (21), where a pneumatic cuff is placed around a limb and inflated suprasystolically to induce an ischemic

environment distal to that cuff. Following a specific amount of time, the cuff is released and the transient elevation in blood flow-associated shear stress induces a vasodilatory response. This response is termed endothelial-dependent flow-mediated vasodilation (FMD). *In vitro* experiments have shown that any change in artery wall shear stress stimulates the endothelial cells to synthesize and release vasoactive substances: increases in shear stress cause the release of vasodilators such as NO, prostacyclin (PGI_2), and endothelial-derived hyperpolarizing factor (EDHF) (29, 59, 132), while decreases in shear stress cause the release of endothelin-1, a potent vasoconstrictor (99). Under very specific procedural conditions, FMD examined through the cuff-occlusion modality has since been shown to elicit strictly a NO-dependent endothelial-mediated response (47, 125). NO is synthesized within the endothelium from L-arginine under the influence of the enzyme endothelial nitric oxide synthase (eNOS). NO has anti-inflammatory and antithrombotic effects and therefore provides a degree of vasoprotection (28, 55). The goal of many human conduit artery FMD studies is to create a shear stress stimulus that evokes a NO dependent FMD response that can provide an assay of NO bioavailability and NO associated vasoprotection (103). To that end, FMD has emerged as a broadly applicable, non-invasive clinically relevant research tool that allows the assessment of endothelium-dependent peripheral artery vasomotion (22, 57, 195).

The Autonomic Nervous System

One of the primary means through which the autonomic nervous system regulates vascular tone and subsequently blood flow is through sympathetic nerve activity (SNA). Exercise leads to an increase in global SNA which affects both the heart (increasing frequency and strength of cardiac muscle contraction) and the blood vessels (producing vasoconstriction). Vasoconstriction is achieved through the release of norepinephrine (NE), which binds to membrane-bound post-junctional α-adrenergic receptors on the vascular smooth muscle. In

the vasculature of exercising muscle, these α-adrenergic receptors are susceptible to the metabolic byproducts originating from the active muscle tissue causing the vascular smooth muscle to be less sensitive to catecholamines (74, 169), and thus, attenuating vasoconstriction. Remensynder *et al.* (158) coined this phenomenon as "functional sympatholysis" and ever since, there is accumulating evidence from both animal and human studies supporting this attenuation of sympathetically-mediated vasoconstriction in exercising skeletal muscle (18, 197, 213). Nevertheless, the underlying mechanisms of sympatholysis are not completely understood, and remain a topic of many ongoing investigations.

Oxidative Stress and Vascular Control

Superoxide anion (O_2^-) and other free radicals are highly energized molecular species, structurally distinct in that they contain one or more unpaired electrons in their atomic orbital (71). Within all mammalian tissue oxidative phophorylation and the formation of ATP is accompanied by the univalent reduction of O_2 to produce O_2^- at an estimated rate of between 2-5% (16, 56). This "electron leakage" is thought to occur at the NADH dehydrogenase (200) and the ubiquinone cytochrome-bc segment of complex III (150) in the mitochondrial electron transport chain. Free radicals are also generated by various oxidases, such as xanthine oxidase, cyclooxygenase, nitric oxide synthase, cytochrome P450, and the Nox family of NAD(P)H oxidases (210).

Oxidative stress is ultimately determined by the balance between pro and antioxidant forces. In low concentrations, free radicals are thought to act as mediators and modulators of cell signaling and contribute to other key functions such as regulating the activity of transcription factors and gene expression (58, 126). In contrast, high levels of free radicals in the vasculature can exceed the local antioxidant defense capacity and thus induce oxidative stress in arterial cells and has been associated with hypertension, atherosclerosis, diabetes,

heart failure, sepsis, as well as the aging process (203). Since the initial observation that superoxide (O_2^-) and other free radicals inactivate NO (208) it has become increasingly apparent that this may contribute to the origin and progression of vascular dysfunction in many of these pathologies (56, 194). Such conclusions are supported by the improvement in endothelial function afforded by the infusion of high levels of exogenous antioxidants in these conditions (54, 116). With the wide ranging impact of oxidative stress in disease and disease progression there is a clear need to better understand the role of free radicals and antioxidants in terms of healthy vascular function.

VASCULAR ADAPTATIONS AND ALTERATIONS

Age-Associated Changes in Vascular Structure and Function

Aging is a relatively non-specific word; in humans, it is particularly difficult to differentiate between manifestations of aging per se and symptoms of disease and disease progression. Rather, it has become increasingly apparent that age-associated changes in cardiovascular structure and function become partners with pathophysiological disease, where aging blood vessels provide the milieu in which disease can flourish. However, over time the human cardiovascular system undergoes many deleterious adaptations, and advancing age has therefore been proposed as a major risk factor for cardiovascular disease, diabetes, hypertension, stroke, atherosclerosis, and congestive heart failure (101). As humans age, changes occur in both the central and peripheral circulation that can affect compliance in arteries and arterioles, arterial blood pressure, and ultimately limit the dynamic capacity of the vasculature (10, 206). Previous studies have documented several factors that preferentially occur in aging populations, including arterial wall thickening (41, 81, 135) and arterial stiffening (95), insulin resistance (119), and increased α-adrenergic (40, 180) and endothelin-1-mediated vasoconstriction (193). However, at the forefront of several functional

investigations has been the age-related reduction in endothelial function affecting vascular tone (17, 205). This is particularly associated with an attenuated NO regulation by the progressive attenuation in eNOS expression, impairment of the nitric oxide pathway, and elevated oxidative stress (2, 7, 184, 194). However, the mechanisms involved in this alteration as well as the extent of these changes are not well defined and probably depend upon the specific etiology.

The Influence of Sex on Vascular Reactivity

The incidence of cardiovascular disease differs significantly between men and women. This is thought to be predominantly due to sex-specific differences in risk factors and the hormonal milieu. Indeed, epidemiological studies have revealed that atherosclerosis, hypertension, peripheral vascular and coronary artery diseases occur with greater prevalence in males and in postmenopausal women when compared to premenopausal females (8, 100, 111). While in clinical assessments of endothelium-dependent peripheral artery vasomotion, FMD studies of healthy populations have revealed that the brachial artery (BA) FMD is more pronounced in premenopausal women than men and their postmenopausal counterparts (112, 142, 176). Therefore, previous studies have implicated estrogen as both a prostaglandin promoter and an antioxidant, protecting nitric oxide from degradation and facilitating increased vasomotion (117, 140). Thus, current thinking knowledge suggests female sex hormones, such as estrogen, have positive vascular effects, whereas their absence could be related to vascular dysfunction and subsequent atherogenic disease states. However, in studies assessing flow-mediated dilation, when the initial value of arterial diameter is taken into consideration, the increase in diameter appears similar between males and females (89). This suggests that some of the documented sex differences in vascular reactivity could be the

consequence of a mathematical bias rather than the beneficial effects of the female hormonal milieu.

Vascular Effects of Exercise Training

It has been well documented and accepted that habitual exercise not only preserves vascular homeostatic mechanisms, but also restores perturbed vascular mechanisms back towards the normal physiological range. Exercise training is associated with an improvement of many cardiovascular and autonomic parameters (9, 14, 77, 84), which are viewed as beneficial adaptations to the physiologic demands of the activity. Elevations in maximal oxygen consumption ($\dot{V}o_{2max}$), a hallmark feature of exercise training, have been attributed to both increases in maximal cardiac output and heightened extraction of oxygen from the arterial blood (25, 107). The beneficial effects of exercise training specifically on the vasculature can be grouped into two forms: structural vascular adaptations and functional vascular adaptations. Structural changes are generally characterized by vascular remodeling (i.e. growth of already-existing vessels) (43, 69) and angiogenesis (15). Functional adaptations are characterized by less neurogenic vasoconstrictor tone (171) and altered local control mechanisms via changes in metabolic control systems (38, 105). Exercise training can augment endothelium-dependent vasodilation by enhancing eNOS expression and therefore increasing NO bioavailability (72). It is also possible that enhanced endothelial function with exercise training is the consequence of a prolonged half-life of NO by reducing its degradation by free radicals or by directly decreasing free radical production (61)

Specific to this thesis are the autonomic adaptations that occur with exercise training. Data in animal models are equivocal regarding the effect of exercise training on limb α-adrenergic responsiveness. In rats, longitudinal training studies have demonstrated decreased sensitivity to sympathomimetics in the trained muscle (209) and no change (52) or decreased

sensitivity (188) in isolated arterial segments. In humans, to our knowledge only two studies have assessed the effect of exercise training on α-adrenoreceptor-mediated vasoconstriction. Smith *et al.* (186) observed similar changes in arm blood flow (venous plethysmography) and arterial blood pressure in sedentary and endurance-trained subjects in response to both sympathomimetic infusion and orthostatic challenge. Similarly, O'Sullivan *et al.* (133) demonstrated a similar degree of vasoconstriction in the forearm of trained and sedentary subjects in response to a 2-min cold-pressor test (CPT). Thus, the present study in both the arm and leg is an effort to extend these earlier findings and elucidate the effect of chronic exercise training upon sympathetically mediated vasoconstriction.

PERSPECTIVES ON LIMB-VASCULAR HETEROGENEITY

Considerable research addressing human skeletal muscle blood flow, vascular reactivity, and muscle metabolism has been performed in isolated limbs of both the upper and lower extremities, but it appears that many of these studies do not have explicit interest in the limb-specific physiological response. The forearm and its vasculature is a good example of a targeted region that has been adopted as much for its practical appeal as its physiological implications. For example, the location and accessibility of the forearm and its vasculature allow vascular reactivity and blood flow measurements to be carefully and relatively easily performed. This has certainly been the case in the clinical context as the development and application of the FMD test has become increasingly, if not almost exclusively, performed in the BA of the arm (31, 76, 125, 148). Indeed, a strong relationship of the BA FMD test and coronary vessel health has been revealed (3, 195). However, the forearm and its vasculature has historically been used as a model to extrapolate findings for the systemic vasculature in humans without the substantial evidence that this is the case (3, 177, 195). Certainly, the perfusion of the forearm may not be of significant consequence to the body as a whole, due to

its relatively small perfused muscle mass. As such, there is a relative paucity of studies that have assessed vascular and metabolic differences with a specific interest in investigating possible limb differences.

To that end, intriguing and clinically significant between-limb heterogeneities have recently become apparent (128, 139, 166). Teleologically, forearm and lower leg differences may be explained by the effects of gravity on limb vascular structure. As upright bipeds, humans are regularly subjected to large hydrostatic and transmural forces in the legs that appear to contribute to decreased capacitance and vascular conductance in the stiffened resistance vessels of the leg (53, 171). The impact of this elevated pressure on vascular control mechanisms in the legs has not been elucidated. However, based on research investigating the effects of elevated blood pressure by the coarctation of the aorta, both endothelial and vascular smooth muscle cell homeostatic processes have been shown to be impaired (12, 136, 202). This model of hypertension resembles the upright condition of the human vasculature where mean arterial blood pressure at the ankle of humans is approximately 65 mm Hg higher than in the arm (171). Therefore, it is plausible that the elevated blood pressure experienced in the lower extremities results in attenuation in vascular reactivity and its homeostatic processes.

It has also been documented that vascular dysfunction due to disease is limb-specific (34, 70, 123, 174), with the lower extremities exhibiting the higher degree of incidence, possibly due to gravity and the subsequently elevated orthostatic stress (53, 171). Therefore, it is important that additional research be conducted to further explore inherent vascular and metabolic limb differences.

Exercise and Limb-Specific Regulation of Muscle Blood Flow

In addition to global cardiovascular improvements, exercise training provokes limb-specific adaptations in vascular function according to the type of exercise performed (36, 73), and even improves vascular function in non-trained limbs (24, 39, 67, 68, 79, 215). DeSouza et al. (39) reported a significant improvement in endothelium-dependent vasodilation to acetylcholine in the arm after 3 months of aerobic exercise training. Studies from our laboratory extend these findings (215), demonstrating a significant, limb-specific improvement in BA FMD, but not in the deep femoral artery (DFA) of the leg after only 6 wk of isolated quadriceps muscle training. The improvement of BA vasodilation after single-leg knee extensor exercise training raises the question of how isolated limb training may produce improvements in vascular beds that do not experience direct, exercise-induced hyperemia. Others (39, 67, 96) have explored this topic, noting improved vasodilatory capacity in untrained limbs after whole body exercise training, which has been attributed to improved NO bioactivity.

In humans, indirect measurements of blood flow in the arm during sympathomimetic infusion and orthostatic challenge (186) as well as cold stimuli (133) have demonstrated a similar degree of forearm vasoconstriction between leg-trained and sedentary subjects in response to the cold-pressor test (CPT). However, in view of the numerous previous studies in the area, it is somewhat surprising how few human studies have specifically assessed training-induced adaptations in sympathetic control of blood flow in trained and untrained limbs.

Aging and Limb-Specific Regulation of Vascular Reactivity and Muscle Blood Flow

Despite our growing understanding of vascular changes with age, several gaps in the literature and newly emerging concepts have clouded this area. Specifically, there appear to

be significant positional-, limb-, and site-specific differences in terms of vascular responsiveness that may blur the assimilation of some age-related studies (128, 216). Aged humans have consistently displayed a 20–30% attenuation in supine resting leg blood flow that has been attributed to ~50% greater leg vascular resistance (42, 44, 118, 124). In addition to supine rest, aging appears to attenuate skeletal muscle blood flow in the leg at submaximal and maximal workloads (10, 86, 110, 145, 147). However, this age-related reduction in blood flow has not been documented in the human forearm (39, 88, 191). As yet unanswered is the question of whether the difference in resting leg blood flow between young and old humans is a consequence of posture, because leg blood flow measurements in human aging studies have always been made while the subject was supine? Also, is blood flow different between young and old subjects during upper extremity exercise? Furthermore, if arm blood flow and leg blood flow are measured in the same subjects, are the putative age-associated decreases in leg blood flow during exercise also seen in the arm?

Recent data from Newcomer et al. (129) in resting subjects utilizing pharmacological interventions suggest that endothelial-dependent vasodilation in the leg is preserved with advancing age, whereas forearm endothelial-dependent vasodilation in the same aged subjects is reduced; although collected at rest, these data imply that endothelial dysfunction is not a likely mechanism for the age-related reduction in leg blood flow during exercise. Although there are no current data to identify a specific mechanism, the fact that leg blood flow and vascular conductance are reduced in specific conditions (supine and exercise) with age, whereas the arm is not affected, may be indicative of age-related and limb-specific changes in vessel structure or alterations in vascular tone. These findings may be mediated by factors such as sympathetic nervous system control (44, 97), endothelin (45), or other potent vasoconstrictors. The apparently nonuniform limb vascular response in healthy young

individuals certainly raises some important questions regarding possible limb-specific alterations that may take place in the aged vasculature.

Limb-Specific Autonomic Control of the Vasculature

In humans, similar degrees of responses have been exhibited in both the arm and leg during acute sympathetic activation (133, 186). In a recent study, Jacob et al. (87) evaluated adrenergic receptor sensitivity (change in vascular resistance) following sympathomimetic drug infusion (phenylephrine and isoproterenol) and the cold-pressor test (CPT) in the arm and leg of younger, normally active volunteers. This study reported a similar increase in local norepinephrine spillover in the arms and legs following the CPT, interestingly the calculated vascular resistance increased in the arm but decreased in the leg, suggesting a limb-specific end-organ response. However, during adrenergic drug infusions in the same subjects the arm demonstrated a greater sensitivity to phenylephrine and a lesser sensitivity to isoproterenol compared with the leg, suggesting that adrenergic-receptor differences cannot explain the paradoxical leg response. This study thus provides convincing evidence for similar sympathetic activation between limbs, but it provides no explanation for the dissociation between sympathetic activation and its functional correlate in the leg.

SPECIFIC AIMS AND HYPOTHESES

Paper I

Aim: To determine the efficacy of an orally administered antioxidant cocktail on free radical concentration and evaluate the antioxidants effects on exercise-induced brachial artery vasodilation in young healthy human subjects.

Hypothesis #1: The antioxidant cocktail will significantly attenuate the circulating free radical signal both at rest and as a consequence of exercise.

Hypothesis #2: In normal healthy subjects a large antioxidant-induced reduction in free radicals will actually attenuate exercise-induced-brachial artery vasodilation.

Paper II

Aim: To examine whether sympathetically mediated vasoconstriction at rest and during acute exercise would differ between sedentary and exercise-trained subjects, and whether these differences would be global or limb-specific.

Hypothesis #1: Sympathetic vasoconstriction in response to the CPT at rest would be attenuated in both the arms and legs of exercise-trained subjects compared to sedentary controls.

Hypothesis #2: In sedentary subjects, acute exercise would attenuate sympathetically-mediated vasoconstriction equally in the arms and legs.

Hypothesis #3: In the exercise trained subjects, sympatholysis would be limb-specific, such that acute exercise would attenuate sympathetically-mediated vasoconstriction to a greater degree in the trained legs compared to the relatively untrained arms.

Paper III

Aim:	To investigate the limb-specific nature of conduit vessel flow-mediated dilation (FMD) and comprehensively evaluate the impact of both a mathematical and experimental normalization technique of the shear rate stimuli between two different vessels.
Hypothesis #1:	The arm (brachial artery, BA) would exhibit a larger FMD than the leg (popliteal artery, PA) when expressed in traditional terms (% change)
Hypothesis #2:	Experimental and mathematical normalization for shear rate would reveal a greater sensitivity (FMD) to a given stimulus level in the leg (PA) than the arm (BA).

Paper IV

Aim #1:	To characterize the post-ischemic cuff hyperemic response in the arm and leg of healthy subjects.
Aim #2:	To characterize skeletal muscle metabolic activity and oxygenation during ischemia and elucidate their influence on muscle blood flow.
Hypothesis #1:	Resting limb blood flow and post-ischemic hyperemia will be similar in the arm and the leg.
Hypothesis #2:	When normalized for muscle mass, both the resting limb blood and the hyperemic response will be far greater in the arm.
Hypothesis #3:	Utilizing multiparametric Nuclear Magnetic Resonance (NMR), we tested the additional hypothesis that the apparent difference in vascular control could be explained by differing skeletal muscle metabolic and/or oxygenation states between limbs.

Paper V

Aim: To determine the effect of aging on blood flow and vascular conductance during exercise in both the upper and lower extremities.

Hypothesis #1: There will be no difference young and old subjects in blood flow during sub-maximal forearm exercise.

Hypothesis #2: The old group will exhibit an attenuated leg blood flow during sub-maximal leg exercise compared to young subjects.

Paper VI

Aim: To evaluate the limb-specific effects of the aging process as it relates to structure, hyperemia, and vascular function of healthy older individuals.

Hypothesis #1: Intima-media thickness (IMT) will be greater in the PA than the BA in both young and old groups and the limb-specific IMT difference will be exaggerated with age.

Hypothesis #2: IR per unit of muscle mass will be attenuated in the lower leg compared to the arm and the IR limb-specific difference will be exaggerated with age.

Hypothesis #3: FMD, expressed in traditional terms (% diameter change), in both the BA of the arm and the PA of the leg will be attenuated in the aged group compared to the young group.

Hypothesis #4: FMD normalized for shear rate will not differ with age in the BA. However, in the PA, normalized FMD will reveal attenuated vascular function in the older group compared to young.

Paper VII

Aim:	To extend previous findings of limb-vascular heterogeneity and the limb-specific regulation of muscle blood flow, but with the added focus of determining the effect of sex.
Hypothesis #1:	IR and FMD will differ between the BA and the PA of both the male and female groups, extending previous findings of limb-vascular heterogeneity.
Hypothesis #2:	Based upon the purported beneficial antioxidant effects of estrogen on NO bioavailability, the impact of a reduced hemoglobin concentration ([Hb]), and smaller baseline vessel diameters in females, ischemic reperfusion and relative FMD will be more pronounced in the arms and legs of the female group.
Hypothesis #3:	When initial vessel diameter and shear rate following cuff occlusion are taken in account (i.e. absolute FMD/shear rate) vascular function in the arms and legs will not be different between males and females.

MATERIALS AND METHODS

SUBJECTS

A total of 140 healthy subjects (122 young (23 ± 2 yrs) subjects (105 males and 17 young females) and 18 old (72 ± 2 yrs) subjects (16 males and 2 females)) participated in these studies. All subjects were nonsmokers, normotensive (<140/90 mmHg), and free of overt cardiovascular disease. Subjects were excluded from participation if they were taking any medications that would alter vascular responsiveness. Young female subjects were studied in the follicular phase (days 1-7) of their menstrual cycle. Three out of the 17 young female subjects were utilizing oral contraceptives. Old female subjects were post-menopausal and not on estrogen replacement therapy. Informed consent was obtained according to the University of California, San Diego, Human Subjects Protection Program requirements. Health histories and physical examinations were completed on all subjects. In addition, graded exercise tests were required for individuals over 40 years of age. All subjects reported to the laboratory in a fasted state (>4 hours postprandial) and had refrained from caffeine and exercise prior to the studies (>12 hours). All studies were performed in a thermoneutral environment.

GENERAL PROCEDURES

Single leg knee-extensor exercise (Papers II and V):

The subject was seated on an adjustable chair with a cycle ergometer (model 828E; Monark Exercise AB, Vansbro, Sweden) placed behind them. Resistance was provided by friction on the flywheel, which was turned by the subject via a metal bar connected to the crank of the ergometer and a boot attached to the ankle of the subject. Sixty dynamic contractions of the knee-extensor muscles per minute were performed (1 Hz). Contractions of the quadriceps femoris muscle caused the lower part of the leg to extend from 90° to 170°

flexion. The momentum of the flywheel assisted in the return of the relaxed leg to the start position. Subjects exercised at work rates of their WR_{max} determined on the preliminary visit. Subjects were allowed sufficient practice during this pre testing to familiarize themselves with the exercise equipment, ensuring that each subject was comfortable with all testing procedures. This modality of exercise is excellent for Doppler studies because the muscles studied are major locomotors, are almost motionless during exercise, and good isolation of this muscle group has been documented (159, 160). Over the past five years we have constructed several versions of single leg knee-extensor ergometers and have published many studies utilizing them (109, 110, 162-165).

Forearm handgrip exercise (Paper I and V):

A single maximal voluntary contraction (MVC) was be established for subjects using a hydraulic handgrip dynamometer with an analog output (Rolyan Ability One, Germantown, WI, USA), and this MVC value was used to calculate an individual relative work rate. During the handgrip exercise, subjects were instructed to squeeze the dynamometer as quickly as possible, which limits the isometric contraction phase to less than 20% of the 2-sec duty cycle (0.5 Hz), resulting in a quasi dynamic exercise modality.

Cold-pressor testing (CPT) (Paper II):

Each CPT was preceded by at least 30 min of supine rest. For all CPT trials, sympathetic activation was accomplished through immersion of the foot in an ice water slurry (1-3 degrees C) for 3 minutes, which has been well documented as a potent reflex stimulus capable of increasing muscle sympathetic nerve activity (130, 178, 179) and plasma norepinephrine levels in both arm and leg (87) without significantly elevating plasma epinephrine (13, 94, 122).

Flow-mediated vasodilation (FMD) (Papers III, IV, VI, and VII):

Subjects lay supine and a pneumatic cuff (Hokanson, Bellevue, WA, USA) was positioned distal to the placement of the ultrasound Doppler probe (arm: upper arm proximal to the elbow, leg: lower right leg below/distal to the knee) visualizing the brachial artery of the arm and the popliteal artery of the leg (152). For leg trials, subjects lay supine on a gurney, modified to allow dorsal ultrasound Doppler access to the popliteal artery. After a 20-min rest period, baseline measurements were made, and the cuff inflated to suprasystolic pressure (>250 mmHg) for 5 min. Full occlusion was documented by the loss of ultrasound spectra in vessels distal to the cuff. When appropriate, arm cuff was inflated to suprasystolic pressure (>250 mmHg) for a period of 30 to ≤ 120 s, to appropriately match the reactive hyperemia and subsequent shear rate observed in the leg FMD study (5 min occlusion).

FMD was calculated as the percent change (relative) or the absolute delta (absolute) from resting artery diameter to the largest diameter achieved during the 105 s of post-inflation imaging. Consistent with the literature, the peak diameter was observed at 50–70 s in most subjects (31). All ultrasound vessel diameter measurements were evaluated during end diastole (corresponding to an R wave documented by the simultaneous ECG signal).

Antioxidant supplementation (Paper I):

All subjects received either an antioxidant cocktail or placebo supplementation in a randomized, double-blind balanced design. The formulation and timing of this antioxidant cocktail was the result of our pilot work employing vascular sampling and electron paramagnetic resonance (EPR) spectral analysis to document its efficacy in reducing free radical concentration, but restrained by the intent to not vastly exceed the common “over the counter” dosage for each individual antioxidant. Consequently, supplements were taken in

two doses separated by 30 minutes, with the first dose ingested two hours before the experimental protocol. The first dose consisted of 300 mg of α-lipoic acid, 500 mg Vitamin C, and 200 I.U. Vitamin E, while the second included 300 mg α-lipoic acid, 500 mg Vitamin C, and 400 I.U. Vitamin E (water dispersible). Placebo microcrystalline cellulose capsules of similar taste, color, and appearance, and was likewise consumed in two similarly timed doses.

MEASUREMENTS

Ultrasound Doppler flowmetry (All Papers):

An ultrasound Doppler (Logiq 7, GE Medical Systems, Milwaukee, Wisconsin, USA) equipped with a linear array mechanical sector transducer operating at an imaging frequency of 8-10 MHz was used to image arterial vessels of the arm and leg. Vessel diameter and intima-media thickness (IMT) was determined at a perpendicular angle along the central axis of the scanned area, where the best spatial resolution was achieved. IMT was twice measured at rest, within close proximity (~0.05 cm), on the far wall, from the interface between blood and intima and the interface between media and adventitia, and then averaged (143). The brachial artery (BA) was insonated 4-8 cm proximal to the antecubital crease, medial to the biceps and brachii muscle. The popliteal artery (PA) was insonated in the popliteal fossa (hollow at the back of the knee) where it was optimally visualized. The common, superficial, and deep femoral arteries (CFA, SFA, and DFA respectively) were insonated distal to the inguinal ligament.

The blood velocity profile was obtained using the same transducer with a Doppler frequency of 5.0-6.7 MHz, operated at high-pulsed repetition frequency mode (2-25 kHz) with a depth of 0.5-3.5 cm in the BA and PA and 1.5-3.5 cm in the CFA, SFA, and DFA. Special care was taken to avoid aliasing, to ensure that probe position was stable, the insonation angle did not vary (60º), and that the sample volume was positioned in the center

of the vessel and adjusted to cover the width of the diameter and therefore the blood velocity

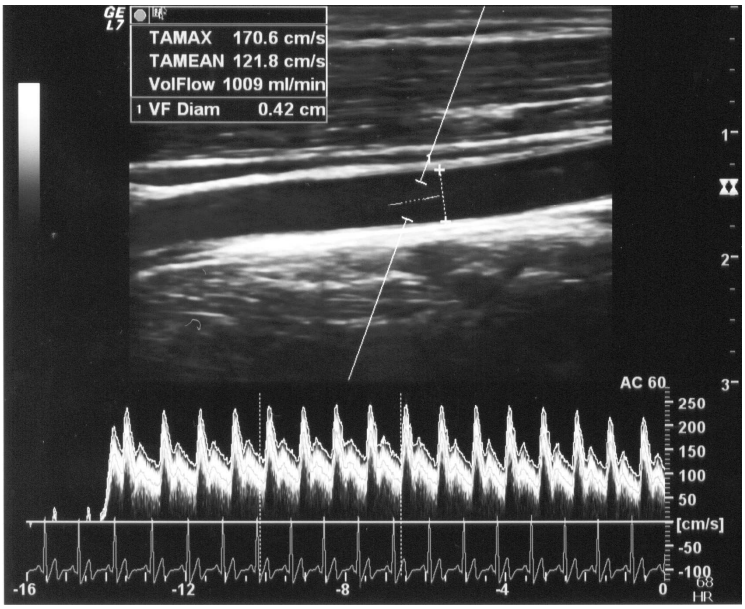


Figure 1. An ultrasound Doppler screen capture illustrating the typical image and blood velocity spectra in the brachial artery following cuff-occlusion release. Note first two cardiac cycles of the Doppler signal are during cuff occlusion, followed by cuff release and subsequent hyperemia. TAMAX is peak veolocity (cm/s), TAMEAN is mean velocity (cm/s), Vol-Flow is blood flow (ml/min), VFDiam is arterial diameter (cm)

distribution. Using arterial diameter and mean velocity (V_{mean}), blood flow was calculated as**:** ***Blood Flow (mL/min)*** $= V_{mean} \cdot \pi \cdot (\text{Vessel Diameter}/2)^2 \cdot 60$**.** Total blood flow (absolute and normalized for muscle mass) was quantified using the area under curve (AUC) for blood flow over time (ml or ml/100g), integrated with the use of commercially available software (SigmaPlot 8.0, Systat Software, Point Richmond, CA). Total blood flow (AUC) were integrated using the trapezoidal rule and was calculated as: $\sum(y_i(x_{(i+1)} - x_i) + (1/2)(y_{(i+1)} - y_i)(x_{(i+1)} - x_i))$

Shear stress has been identified as a mechanism that stimulates the vascular endothelium and results in subsequent vasodilation (144). However, as blood viscosity was not be measured, shear rate was calculated by using the equation (34, 215, 216): ***Shear rate*** $(s^{-1}) = 4 \cdot V_{mean}$***(cm/s) / Vessel diameter(cm).*** Cumulative shear rate was expressed using the area under the curve (s^{-1}•s) for shear rate over time (1, 148), integrated with the use of commercially available software (SigmaPlot 8.0, Systat Software, Point Richmond, CA). Cumulative shear rate area under the curves was again integrated using the trapezoidal rule.

Multiparametric nuclear magnetic resonance (NMR) (Paper IV):

These studies were carried out in a 4 Tesla, 46-cm internal bore, superconducting magnet (Magnex 4/60) interfaced to a Bruker Biospec NMR spectrometer. Muscle perfusion, intracellular oxygenation, and energy metabolism was studied simultaneously by rapidly interleaved acquisitions of saturation inversion recovery Arterial Spin Labeling (ASL) perfusion imaging, ^{1}H spectroscopy of deoxymyoglobin, and ^{31}P spectroscopy of the high-energy phosphate metabolites (49). The subject's appropriate limb was carefully positioned inside a 17 cm inner diameter transversal electromagnetic ^{1}H transmit-and-receive volume coil, and an 8-cm diameter custom built ^{31}P surface coil slid underneath the limb.

Arterial Spin Labeling (ASL). A temporary perfusion map was extracted by summing the differences between successive pairs of images acquired at rest, 5 minutes of arterial occlusion, and 100 seconds following release. Multiple (2-3) regions of interest (ROIs) each with an area ~2-3 cm^2 were traced within the lower leg and the forearm, randomly sampling the total area but carefully excluding voxels containing lipids or vessels. Identical ROIs were selected in all the images of the series, and perfusion (f) was calculated according to the equation (156):

$$f = -\frac{\lambda}{T}\cdot\left\{\frac{M_{SS}(T)-M_{NS}(T)}{M_{SS}(T)+M_{NS}(T)}\cdot\left[1-\exp(r1\cdot T)\right]+1\right\}$$

where M stands for the image intensity in muscle ROI after slice-selective and nonselective inversion; T is the ASL time (0.82 s); λ is the tissue/blood partition coefficient (0.9), and r1 is the muscle spin-lattice relaxation rate (0.66 s^{-1}).We have previously described in detail the quantitative relationship between perfusion and the MRI signal (19, 60, 211, 212).

^{1}H Deoxymyoglobin. After a 100-Hz line-broadening exponential multiplication and Fourier transformation, zero- and first-order phases of the deoxy-Mb spectrum were adjusted manually on an end-cuff acquisition. All FIDs of the series were processed using these same parameter settings. After automatic baseline correction (± 20 ppm), the deoxy-Mb peak of each spectrum was quantified by integration over 10 ppm. Fractional deoxy-Mb signal was determined by normalizing these data to the maximal deoxy-Mb spectra observed at the end-cuff acquisition, assuming complete desaturation in 4-6 min (163, 199, 207). To appropriately account for the potential impact of muscle mass or limb myoglobin concentration, fractional deoxy-Mb was then normalized to limb muscle mass (deoxy-Mb (AU)/ muscle mass (100 g)). Myoglobin desaturation rate was determined by the slope of the linear portion of the deoxy-Mb kinetic curve between 90-180 s during ischemic cuff-occlusion.

^{31}P Spectra of High-Energy Phosphates. The ^{31}P FIDs were processed in a similar fashion to the ^{1}H spectra, except for an 8-Hz line-broadening exponential multiplication. Inorganic phosphate (P_i) and phosphocreatine (PCr) integration limits were set to 5.6/3.5 ppm and 1.5/-1.5 ppm, respectively. Muscle intracellular pH was calculated from the chemical shift (δ) between the P_i and PCr peaks (196):

$$\mathrm{pH} = 6.75 + \log\left[\frac{-3.27 + \delta}{5.69 + \delta}\right]$$

Spin trapping and Electron Paramagnetic Resonance (EPR) spectroscopy (Paper I):
EPR was performed on venous blood samples. Briefly, 4.5ml of venous blood was collected into a vacutainer that contained 1.5ml of the spin trap α-phenyl-tert-butylnitrone (PBN) (0.140mol/L). After centrifugation, the PBN adduct was extracted from the serum supernatant with toluene, and the adduct (200 µL) was pipetted into a precision-bore quartz EPR sample tube (Wilmad Ltd, UK) that had been flushed with compressed N_2. EPR was performed at 21

°C using an EMX X-band spectrometer (Bruker, MA, USA) using commercially available software (Bruker Win EPR System, Version 2.11), with data processing blinded to experimental condition (achieved by coded numbering of samples).

Heart rate (All Papers):

Heart rate was recorded from a standard 3-lead ECG, an integral component of the Doppler system (Logiq 7, GE Medical Systems, Milwaukee, Wisconsin, USA).

Noninvasive blood pressure (All Papers):

During studies using the Doppler system, blood pressure was measured using radial tonometry (Biopac Systems NIBP 100A), which calculates systolic and diastolic and mean pressures derived from a pressure sensor placed directly above the radial artery.

Tissue volume measurements (Papers II, and IV-VII):

Forearm and lower leg circumferences (distal, proximal end, and one-third distal to the proximal end) and length (joint-to-joint) were measured to calculate tissue volume (92). Additionally, ventral (forearm, quadriceps) and dorsal (lower leg) skinfold measurements were taken to assess subcutaneous fat and allow the calculation of muscle volume for the quadriceps, lower leg and forearm (46, 92, 149).

Muscle mass of the complete forearm (Papers II, and IV-VII) and lower leg (Papers II, and IV, VI, and VII) was calculated from the anthropometric assessment of muscle volume by multiplying by the density of muscle (1.06 g/cm^3). On the basis of both an excellent agreement (forearm: ±5%, lower leg: ±2%) and a high correlation (forearm: r = 0.91, lower leg: r = 0.92) between this method and dual energy X-ray absorbometry (Explorer; Hologic, Waltham, MA) documented previously in our laboratory for the forearm

(46) and recently (unpublished observations, (n=10)) in the lower leg, we applied the following regression equations to the anthropometrically determined values for the forearm and the lower leg:

Forearm: muscle mass (anthropometric) (kg) · 1.155 - 0.24 = Muscle mass (kg)

Lower Leg: muscle mass (anthropometric) (kg) · 1.0271 - 0.0064 = Muscle mass (kg).

Thigh muscle volume (Paper II and V) was converted to quadriceps muscle mass with the use of the following equation: *Thigh muscle volume (L) · 0.307 + 0.353 = thigh muscle mass.* This anthropometrically determined quadriceps muscle mass, previously revealed to correlate highly with muscle mass assessed by computer tomography (r^2 = 0.86), was corrected on the basis of this relationship with the following equation (149): *Muscle mass (anthropometric)(kg) · 0.924-0.292 = quadriceps muscle mass (kg).* It should be noted that these calculations do not remove the volume occupied by bone.

Statistics:

Statistics were performed using commercially available software (SigmaStat 3.10, Systat Software, Point Richmond, CA). Repeated-measures ANOVA, ANOVA, and Student's *t*-tests were used to identify significant changes in variables within and between age groups and limbs, with the Student-Newman-Keuls test used for post hoc analysis when a significant main effect was found. All group data are expressed as mean ± SE. Statistical significance was established at $P < 0.05$.

SUMMARY OF RESULTS

Paper I

Electron Paramagnetic Resonance (EPR) spectroscopy revealed a reduction in circulating free radicals following antioxidant administration at rest (~98%) and as a consequence of exercise (~85%) (Figure 2).

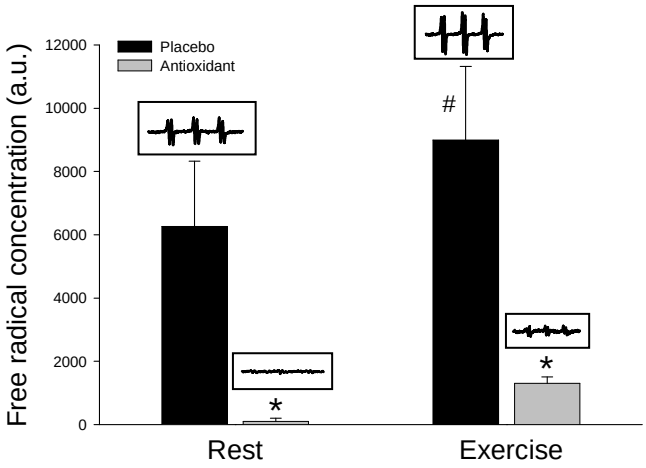
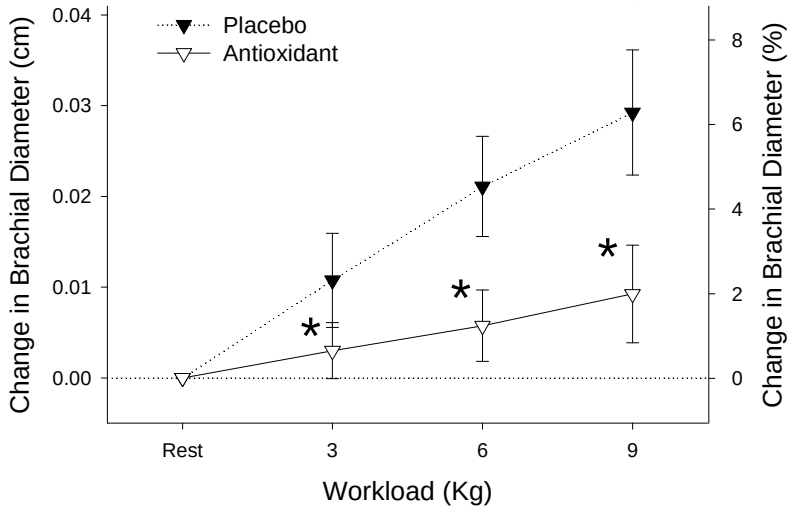


Figure 2. The alpha-phenyl-tert-butylnitrone (PBN) electron paramagnetic resonance (EPR) spectroscopy data under the conditions of rest and following exercise with placebo and the oral antioxidant cocktail. Inlayed are representative individual examples of the PBN EPR spectra under each scenario.

Plasma total antioxidant capacity and vitamin C both increased following the ingestion of the antioxidant cocktail, whereas vitamin E levels were not influenced by the ingestion of the antioxidants. Brachial artery vasodilation during submaximal forearm handgrip exercise was greater with the placebo (7.4 ± 1.8%) than with the antioxidant cocktail (2.3 ± 0.7%) (Figure 3).

Figure 3. The effect of an oral antioxidant cocktail on change in brachial artery diameter in young healthy subjects at rest and at three submaximal levels of handgrip exercise (3, 6, and 9 kg at 0.5 Hz). Values for % change in brachial diameter are not exact and are displayed solely for reference purposes (right axis). * significantly different from the placebo condition.



Paper II

At rest, the cold-pressor test (CPT) decreased vascular conductance similarly in the leg and arm of sedentary subjects (–33 ± 8% leg, –38 ± 6% arm) and cyclists (–34 ± 4% leg, –31 ± 9% arm) (Figure 4), and during exercise CPT-induced vasoconstriction was blunted (i.e.,

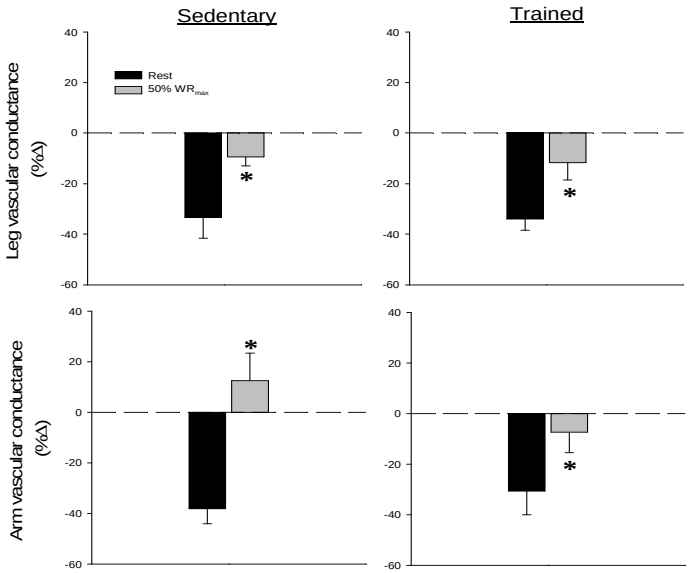


Figure 4. Changes in calculated vascular conductance from pre-CPT values during a 3-min CPT at rest (solid black bars) and during exercise at 50% of WR_{max} (solid gray bars) in leg (*top*) and arm (*bottom*) trials in sedentary and cyclist groups. Values are means ± SE. %Δ, Percent change. *Significantly different from resting CPT trial, $P < 0.05$.

sympatholysis) in both the leg and arm of both groups. However, the magnitude of sympatholysis was significantly different between the arm and leg of the sedentary group (–47 ± 11% arm, –25 ± 8% leg), and it was less in the arm of cyclists (–28 ± 11%) than sedentary controls (Figure 5).

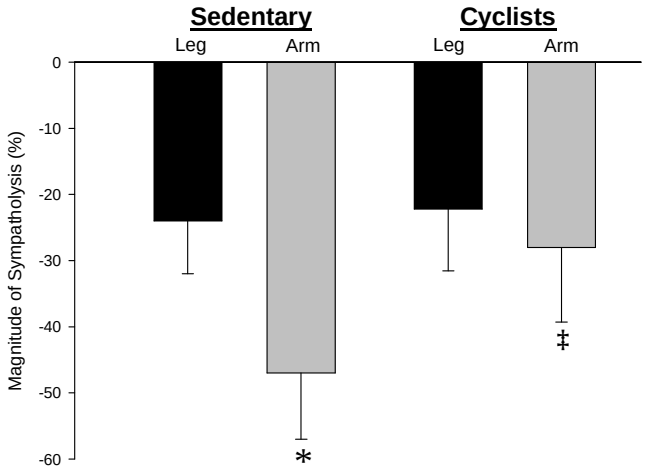


Figure 5. "Magnitude of sympatholysis" in the leg and arm of the sedentary and cyclist groups, i.e., the calculated difference in vascular conductance changes between rest and exercise to the CPT. Values are means ± SE. * Significantly different from leg ($P < 0.05$). ‡ Significant difference between sedentary and cyclist groups, ($P < 0.05$).

Paper III

The brachial artery (BA) revealed a smaller diameter and larger post-ischemic cumulative blood velocity (area under curve, AUC) than the popliteal artery (PA), a combination that resulted in an elevated post-cuff cumulative shear rate (AUC) in the BA (BA: 25419 ± 2896 s^{-1}•s; PA 8089 ± 1048 s^{-1}•s, $P < 0.05$) (Figure 6A). Thus, when expressed in traditional terms

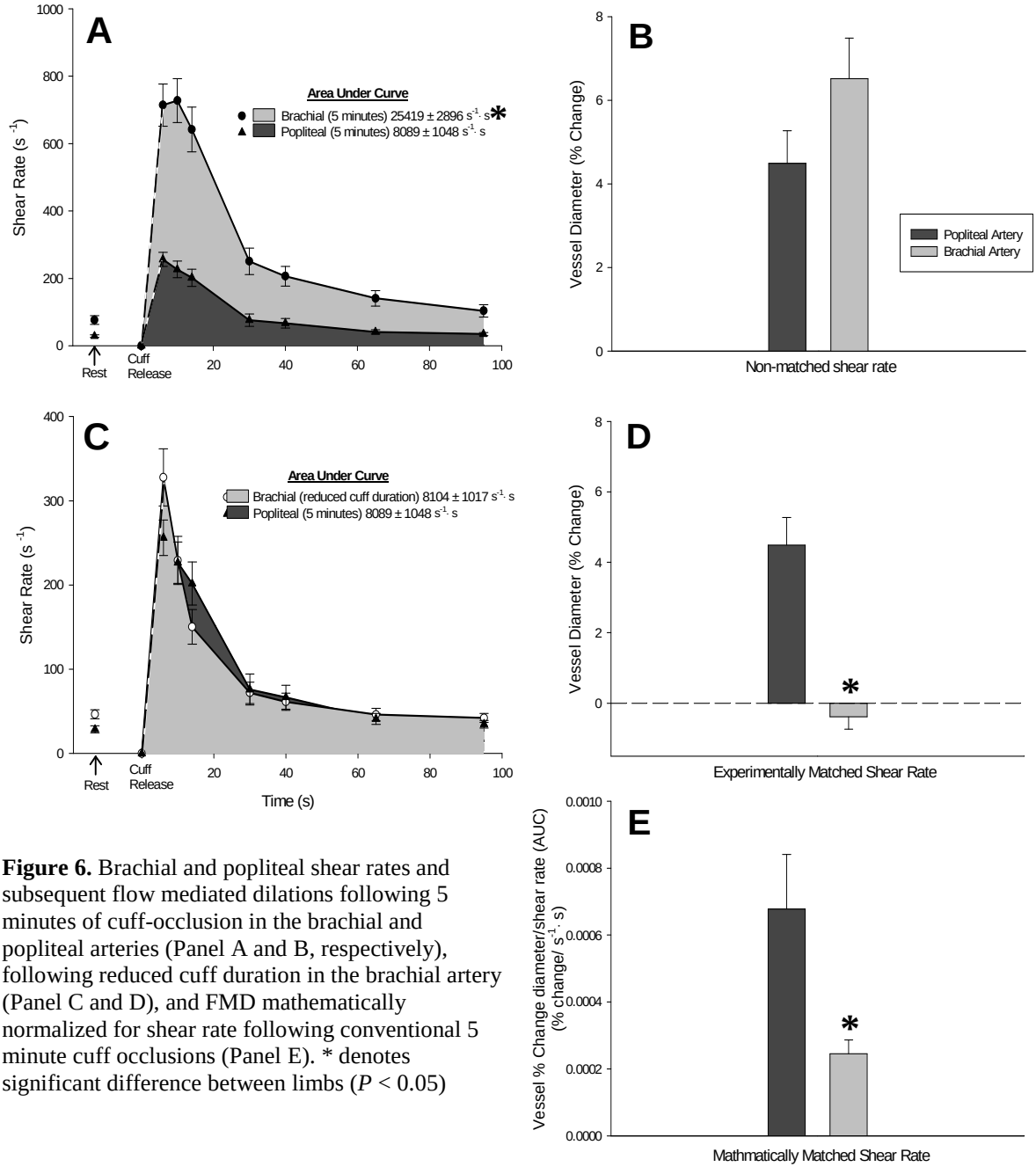


Figure 6. Brachial and popliteal shear rates and subsequent flow mediated dilations following 5 minutes of cuff-occlusion in the brachial and popliteal arteries (Panel A and B, respectively), following reduced cuff duration in the brachial artery (Panel C and D), and FMD mathematically normalized for shear rate following conventional 5 minute cuff occlusions (Panel E). * denotes significant difference between limbs ($P < 0.05$)

there was a tendency for the BA to have a greater FMD than the PA (6.5 ± 1.0% and 4.5 ± 0.8%, respectively; $P = 0.1$) (Figure 6B). Due to an elevated shear rate in the BA compared to the PA for the 5 min cuffing experiment, average cuff duration during experimental shear rate matching protocols in the arm was significantly reduced from 5 min to 60 ± 9 s. Both individually and therefore on average, matching of shear rate was achieved (5 min cuff PA cuff-occlusion: 8089 ± 1048 s^{-1}•s, BA reduced cuff duration: 8104 ± 1016 s^{-1}•s) (Figure 6C). When shear rate was experimentally matched (PA: 4.5 ± 0.8%; BA: -0.4 ± 0.4%) (Figure 6D) or mathematically normalized; (PA: $6.8\times10^{-4} \pm 1.6\times10^{-4}$ %Δ/ s^{-1}•s; BA: $2.5\times10^{-4} \pm 0.4\times10^{-4}$ %Δ/ s^{-1}•s) (Figure 6E) the PA revealed a greater FMD per unit of shear rate than the BA ($P < 0.05$).

Paper IV

In absolute terms, both resting and cumulative blood flow (AUC)) over 105 s following cuff release was not different between the forearm and lower leg (Figure 7A). However, when appropriately expressed relative to muscle mass, blood flow was significantly different between limbs at rest (forearm: 10 ± 1; leg: 4 ± 0.5 ml/100g, $P<0.05$) and during ischemic reperfusion (IR) (forearm: 55 ± 4; leg: 17 ± 2 ml/100g AUC, $P<0.05$) (Figure 7B). To extend these limb-specific vascular findings and to examine potential contributing mechanisms, 6 subjects were studied utilizing multiparametric nuclear magnetic resonance to simultaneously examine muscle perfusion (arterial spin labeling (ASL)), intracellular de-oxygenation (myoglobin proton spectroscopy), and muscle metabolism (phosphorous spectroscopy (^{31}P)). Metabolic perturbation, muscle pH, and de-oxygenation rates during cuffing were not different between limbs. However, ASL (AUC) confirmed the resting blood flow differences between limbs (forearm: 16 ± 4; leg: 6 ± 1 ml/100g, $P<0.05$) which were maintained, albeit at a lesser degree, during IR (forearm: 47.1 ± 6.1; leg: 29.2 ± 2.9 ml/100g, $P<0.05$) (Figure 7C).

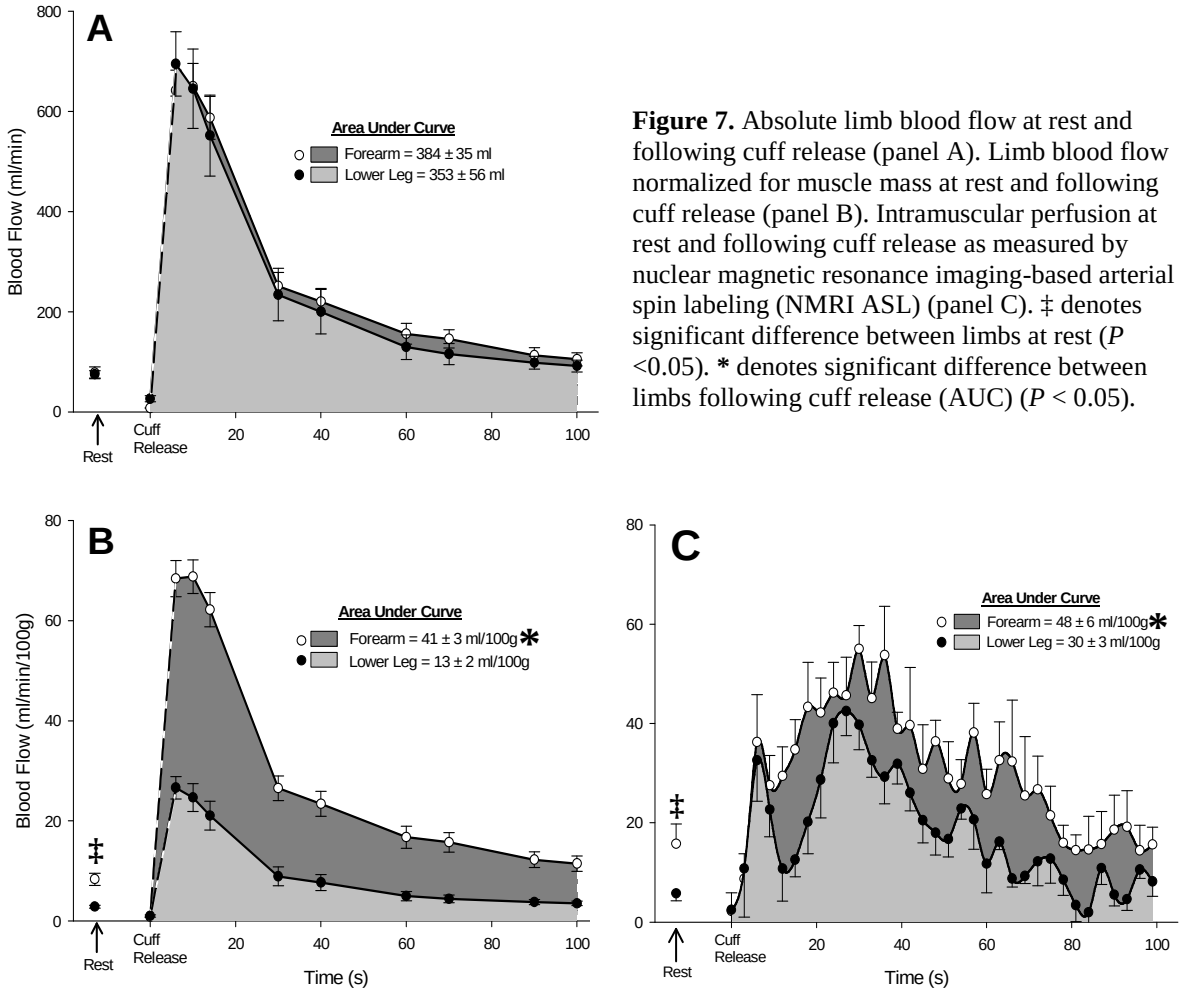


Figure 7. Absolute limb blood flow at rest and following cuff release (panel A). Limb blood flow normalized for muscle mass at rest and following cuff release (panel B). Intramuscular perfusion at rest and following cuff release as measured by nuclear magnetic resonance imaging-based arterial spin labeling (NMRI ASL) (panel C). ‡ denotes significant difference between limbs at rest (P <0.05). ***** denotes significant difference between limbs following cuff release (AUC) (P < 0.05).

Paper V

Quadriceps muscle mass was significantly different between young (2.1 ± 0.2 kg) and old subjects (1.6 ± 0.1 kg) (P<0.05). During exercise, blood flow and vascular conductance in the leg were attenuated in the old when expressed as blood flow per unit muscle mass for a given absolute workload or at a given relative exercise intensity (young, 1,523 ± 329; old, 1,340 ± 157 ml·kg^{-1}·min^{-1} at 40% WR_{max}) (Figure 8B). In contrast, aging did not affect forearm muscle mass or attenuate exercise blood flow or vascular conductance in the arm (Figure 8A)

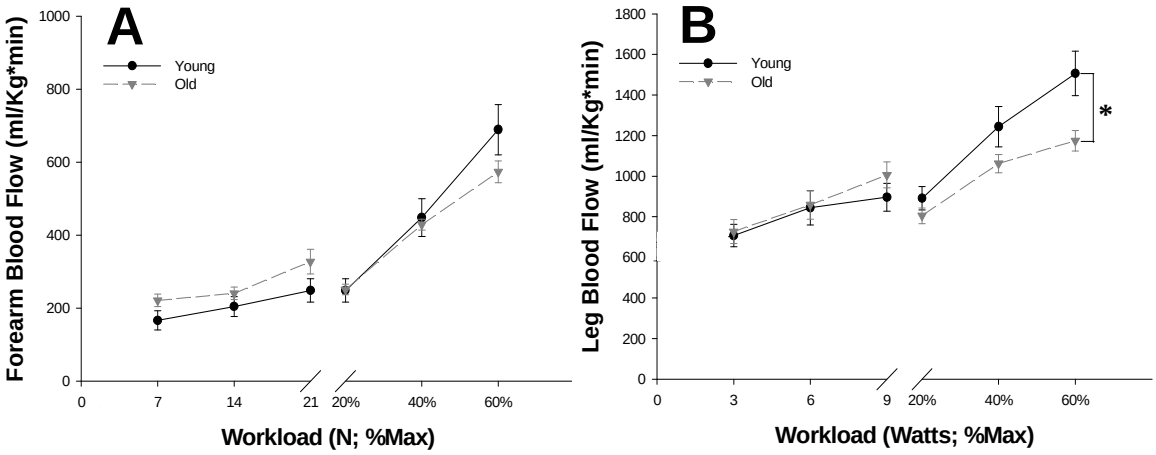


Figure 8. Effects of aging on blood flow per kilogram of forearm muscle mass (panel A) and of quadriceps muscle mass (panel B) during exercise across a series of submaximal absolute and relative workloads (handgrip at 0.5 Hz, knee-extensor 1Hz) in young and old subjects. * denotes significant difference between young and old

Paper VI

Intima-media thickness (IMT) measurements revealed a "thickening" in the popliteal artery (PA) compared to the brachial artery (BA) which was exaggerated with age (young: BA: 0.028 ± 0.001 and PA: 0.046 ± 0.003, old: BA: 0.039 ± 0.002 and PA: 0.073 ± 0.005 cm; $P < 0.05$) (Figure 9). IR revealed a similar pattern as IMT in terms of limb and age-related differences.

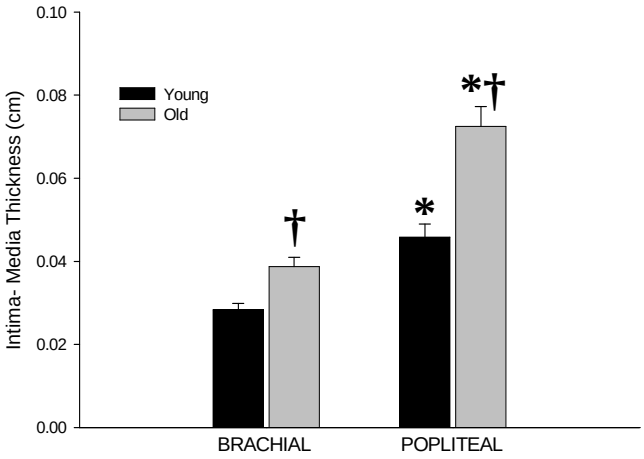


Figure 9. Brachial and popliteal artery intima-media thickness in young and old subjects. * denotes significant differences between limbs ($P < 0.05$). † denotes significant differences between young and old ($P < 0.05$).

There was an age-related attenuation in both BA FMD (young: 7.4 ± 0.8%, old: 4.6 ± 0.6%; $P < 0.05$) and PA FMD (young: 5.5 ± 0.6%, old: 1.6 ± 0.5%; $P < 0.05$) (Figure 10A).

However, when this % change was normalized for shear rate, only the PA FMD of the old group was still significantly attenuated (young: 10.0 $\times 10^{-4} \pm 1.5 \times 10^{-4}$, old: 5.8 $\times 10^{-4} \pm 1.9 \times 10^{-4}$ % Δ / s^{-1}•s) (P <0.05) (Figure 10B).

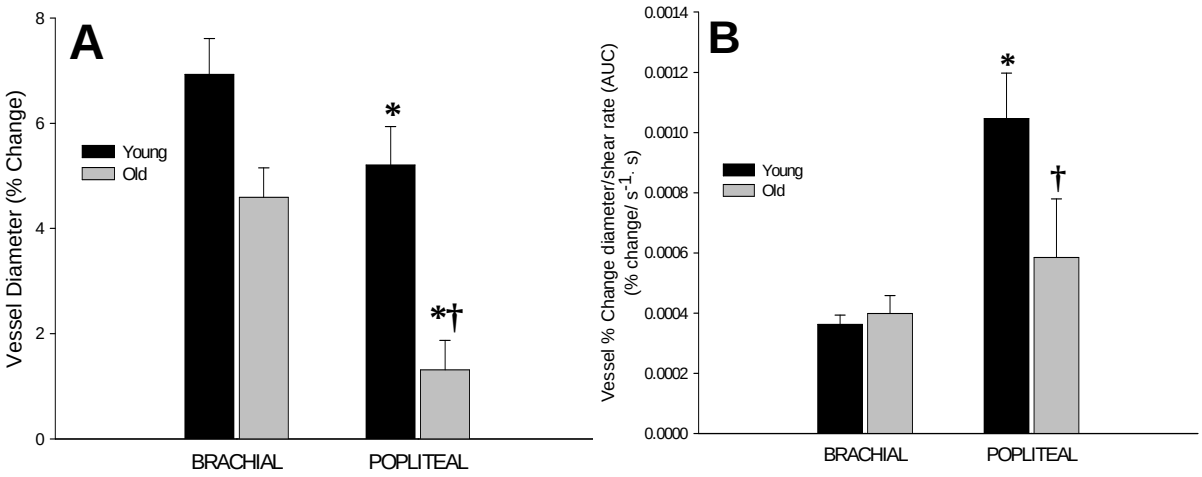


Figure 10. Brachial and popliteal artery flow-mediated dilation in young and old subjects expressed as % change in diameter (panel A) and normalized for the shear rate stimulus (panel B). * denotes significant difference between brachial artery and popliteal artery ($P < 0.05$). † denotes significant difference between young and old groups ($P < 0.05$). Note the similar brachial artery flow-mediated dilation normalized for shear rate between young and old groups, whereas the same normalization for shear in the popliteal artery does not correct the attenuated dilation (panel B).

Paper VII

Between the sex groups, relative FMD (% diameter change) was significantly larger in the female group for the BA (male: 6.7 ± 0.6%, female: 8.7 ± 1.1%; $P < 0.05$) and was not statistically different in the PA (male: 4.4 ± 0.6%, female: 5.4 ± 0.8%) (Figure 11A). When relative FMD was normalized for the shear rate AUC, the PA of both limbs revealed no sex-related differences (Figure 11C) (male group: PA: 8.3 × 10^{-4} ± 0.1 ×10^{-4} and BA: 3.8 × 10^{-4} ± 0.3 × 10^{-4} % Δ / s^{-1}•s, $P < 0.05$; female group: PA: 7.5 × 10^{-4} ± 1.6 × 10^{-4} % Δ / s^{-1}•s and BA: 3.5 × 10^{-4} ± 0.5 × 10^{-4} % Δ / s^{-1}•s, $P < 0.05$) (Figure 11C).

With the statistically smaller resting diameters in the female group for both BA and PA, FMD was also assessed as an absolute change in diameter. Using this approach, there was no statistical difference both within and between limbs and sex groups (male group: BA:

0.027 ± 0.002 and PA: 0.027 ± 0.003 cm, female: BA: 0.027 ± 0.003 and PA: 0.024 ± 0.003 cm) (Figure 11B). Consistent with the relative FMD, when absolute FMD was normalized for

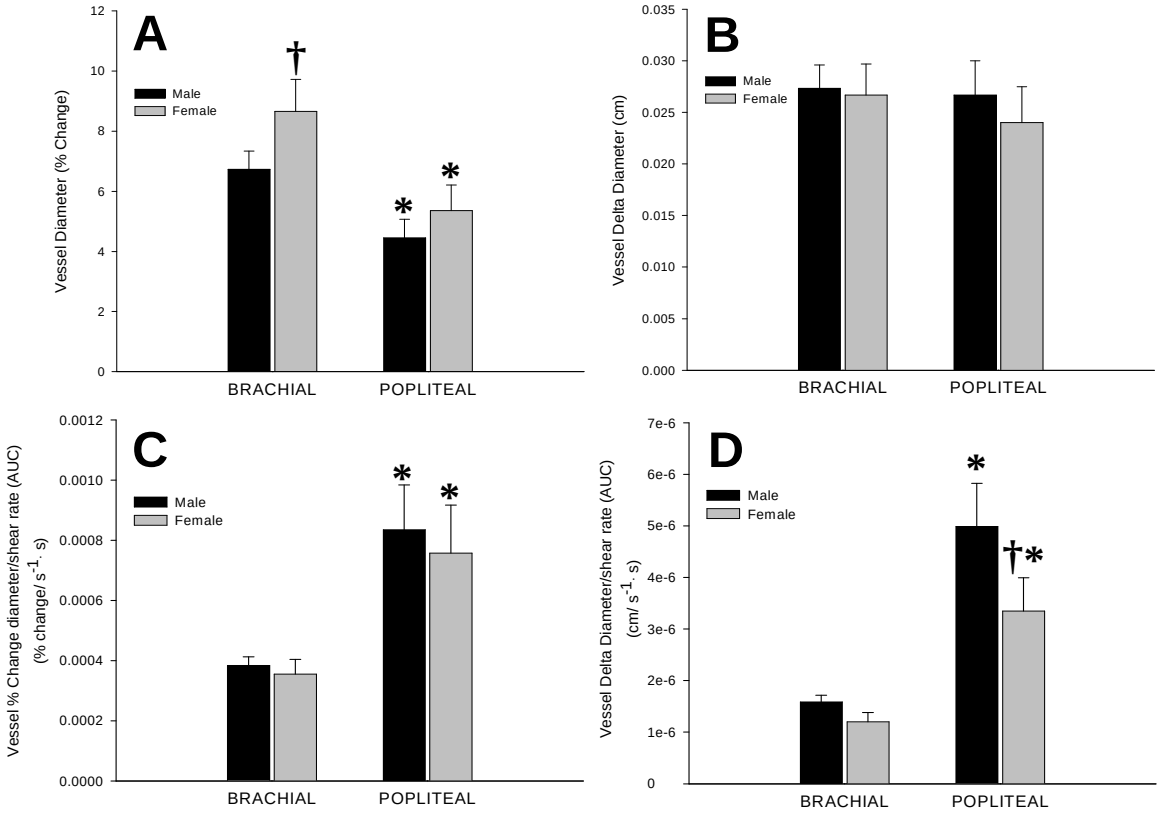


Figure 11. Brachial and popliteal artery flow-mediated dilation (% diameter change (panel A) and absolute diameter change (panel B)) in male and female subjects. Flow-mediated dilation normalized for shear rate area under curve (% diameter change (panel C) and absolute diameter change (panel D)). * denotes significant difference between brachial artery and popliteal artery ($P < 0.05$). † denotes significant difference between male and female ($P < 0.05$).

the shear rate AUC, the PA of both the male and female groups revealed a significantly greater FMD for a given shear rate than their respected BA's (male group: PA: $5.0 \times 10^{-6} \pm 0.8 \times 10^{-6}$ and BA: $1.6 \times 10^{-6} \pm 0.1 \times 10^{-6}$ cm / s^{-1}•s, $P < 0.05$; female group: PA: $3.3 \times 10^{-6} \pm 0.6 \times 10^{-6}$ and BA: $1.2 \times 10^{-6} \pm 0.2 \times 10^{-6}$ cm / s^{-1}•s, $P < 0.05$) (Figure 11D). In contrast to the relative FMD/shear rate AUC, there was a sex-related difference in PA absolute FMD/ shear rate AUC ($P < 0.05$), but no sex-related difference in BA absolute FMD/Shear Rate AUC (Figure 11D).

DISCUSSION

THE INFLUENCE OF OXIDATIVE STRESS ON VASCULAR FUNCTION DURING EXERCISE (Paper I)

Pro- and Antioxidant Forces

The delicate balance between pro- and antioxidant forces and the subsequent positive versus negative effects of free radicals is likely a crucial aspect of life (48). Low concentrations of free radicals appear to have both important mediating and modulating roles in cell signaling (48, 58, 126); however, without restraint higher levels of free radicals such as O_2^- can cause a wide spectrum of cellular damage, including lipid peroxidation, alteration of intracellular redox state, inactivation of enzymes, and damage to DNA. Consequently, there are numerous endogenous antioxidants that act as a defense system against oxidative stress. These antioxidants are generally divided into the nonenzymatic antioxidants (e.g. antioxidant vitamins) and the enzymatic antioxidants (e.g. SOD). Under normal circumstances the endogenous array of antioxidants combine to minimize, but, as evidenced in the current study by EPR spectroscopy, there is some normal background level of oxidative stress *in vivo* which is magnified by exercise (Figure 2). However, the acute ingestion of an antioxidant cocktail effectively ablated the blood-borne alkoxyl and alkyl radicals at rest and severely attenuated them following exercise (Figure 2). These EPR data certainly are indicative of the more "classical," although indirect, markers of peroxidation and provide clear evidence for peroxidative stress and its reduction with the antioxidant cocktail. The direct assessment of increased plasma total antioxidant capacity and vitamin C further validate this acute oral approach to tipping the balance away from pro-oxidant forces. With such an aggressive and clearly documented reduction in free radical concentration, the stage is set to determine the role of oxidative stress in the vascular response to exercise.

Exercise, Oxidative Stress, and Antioxidants

In terms of the link between oxidative stress and vascular function, it is well accepted that free radicals likely limit vasodilation and blood flow by reducing NO bioavailability (54); however, it is also plausible that some free radicals and their end products increase vasodilation via their direct vasoactive properties (114). Clearly, the current data support the latter concept, because the large antioxidant-induced reduction in free radical concentration (Figure 2) resulted in a diminished vasodilatory response to exercise in the brachial artery (Figure 3). To our knowledge these are the first data to directly reveal that "unbalancing" the equation through a documented reduction in free radicals (and an increase in plasma antioxidants) in normal healthy subjects during exercise negatively impacts exercise-induced vasodilation (Figure 3). These data reveal a potentially important role for oxidative stress in provoking an appropriate vasodilation during exercise. We speculate that this attenuated exercise-induced vasodilation is likely the direct result of disturbing the natural balance between pro- and antioxidant forces. The downstream consequences of free radicals such as H_2O_2 and $ONOO^-$, perhaps released in response to increased shear stress, may act as potent vasodilators (11), and as such possess the capacity to alter vascular responsiveness (114). Thus it is likely that the large and clearly documented reduction in free radical concentration following antioxidant administration (Figure 2) may have removed oxidative species, which possess some beneficial vasoactive properties, severely attenuating the exercise-induced brachial artery vasodilation following antioxidant ingestion.

AUTONOMIC CONTROL OF MUSCLE BLOOD FLOW (Paper II)

Limb-Specificity and Sympathetic Vasoconstriction at Rest and During Exercise

The cold-pressor test (CPT) was utilized to provoke a profound reflex increase in sympathetic nerve activity (108), with subsequent changes in heart rate, arterial blood

pressure, and blood flow. Expression of sympathetic activation in response to the CPT has been well documented, with others demonstrating a robust (>300%) increase in muscle sympathetic nerve activity (131, 178) that does not differ between limbs (173, 181). Similarly, the CPT elevates venous norepinephrine levels to a similar degree 40–60% in both the arms and legs (26, 83, 87). These similarities in sympathetic activation between limbs set the stage to explore the end-organ translation of sympathetic activation into vasoconstriction, which to our knowledge has not been investigated utilizing ultrasound Doppler.

Others have recognized vascular limb specificity in response to orthostasis (85), and sympathomimetics (87, 139). The current study supports the concept that sympathetically mediated vasoconstriction provoked by the CPT is expressed systemically at rest in the peripheral circulation (157), with no apparent selectivity of this response between limbs (Figure 4).

Although sympathetic activation is fully expressed in resting muscle, recent studies indicate that this response may be blunted in the exercising limb, an event know as functional sympatholysis (197). In further support of this concept, we observed smaller changes in both arm and leg vasoconstriction during acute exercise compared with the resting CPT (Figure 4). These data extend recent observations by Koch et al. (97) that leg Q did not change when the CPT was applied to young subjects during upright cycling, although this study did not include a resting CPT trial for comparison. Thus, to our knowledge, this is the first report of a blunted sympathetic vasoconstriction in response to the CPT during limb-specific exercise in humans.

Exercise Training and Sympathetic Vasoconstriction

Although several cross-sectional (179, 190) and longitudinal (153, 183) studies have suggested that regular exercise training does not significantly change resting MSNA, we hypothesized that the actual expression of sympathetic activity would be lessened due to

limb-specific, training-induced changes in end-organ (i.e. α-adrenoreceptor) function. The present findings extend earlier findings, demonstrating that chronic exercise training does not alter resting sympathetically mediated vasoconstriction to either trained or untrained limbs in young, healthy subjects (Figure 4).

Others have reported that exercise training results in a reduction in the expression of sympathetic nerve activity in muscle during acute knee-extensor (153) and handgrip (187) exercise, a response that appears to be limited to the trained limb (183). Thus one focus of the present study was to identify potential limb-specific responses to sympathetic vasoconstriction within both sedentary and exercise-trained subjects during acute exercise. Although leg Q and vascular conductance were significantly higher in cyclists than sedentary subjects during knee-extensor exercise (due to the higher absolute work rate), the CPT during exercise did not cause significant change in absolute leg vascular conductance in either group. These responses resulted in a similar calculated magnitude of sympatholysis between sedentary (–24 ± 8%) and cyclists (–22 ± 9%) (Figure 5). In contrast to the leg, the magnitude of vasoconstriction in the arm during exercise compared with rest differed according to training status. When vascular conductance changes were expressed as percent changes, the magnitude of sympatholysis in the arm was significantly greater in the sedentary group (–47 ± 11%) than in the cyclists (–28 ± 11%) (Figure 5). From these results, it appears that vasoconstriction in the arm of the cyclists is somewhat less inhibited (i.e., more sympathetic vasoconstriction during exercise) than the sedentary group during exercise. We speculate that this response may be due to increased α-adrenergic sensitivity, similar to animal data demonstrating increased adrenergic vasoconstriction in the untrained (spinotrapezius) skeletal muscle of treadmill trained rats (104). Conceptually, this observed decrease in arm sympatholysis compared with the sedentary group may represent a training adaptation related to end-organ sensitivity designed to ensure optimal distribution of Q to the exercising legs,

and it may serve to prevent possible overperfusion of the arm and potential blood flow "steal" from the legs. However, further studies with measurements at multiple exercise intensities are needed to determine the mechanism responsible for this intriguing response in the relatively untrained limb of competitive cyclists.

FLOW-MEDIATED DILATION AND ISCHEMIC REPERFUSION IN YOUNG HEALTHY INDIVIDUALS: ARE ALL LIMBS CREATED EQUAL? (Papers III and IV)

Flow-Mediated Dilation (FMD)

The FMD technique, first employed by Celermajer *et al.* (21), has emerged as a broadly applicable, non-invasive clinical tool to study endothelium-dependent peripheral artery vasomotion (22, 57, 195). In their original work and in the current study, a 5 minute or less cuff occlusion was employed with the aim of eliciting strictly a NO-dependent endothelial-mediated response (47, 125). However, it was not until recently that the importance of the shear stress stimulus and its non-uniformity across subjects and studies was recognized, leading to a need to accurately manipulate or correct for this force (121, 148). Some have characterized shear stress as a peak attained after cuff release and used this variable to normalize FMD for the stimulus (34, 138). However, it has become increasingly apparent that the peak shear rate may not reflect the true nature of the shear stimulus. Therefore the area under the curve (AUC) for shear rate across time (s^{-1}•s) has gained favor as the most appropriate approach to quantify the cumulative stimulus contributing to the vasodilatory response (148). In the current studies we adopted this approach and applied it accordingly, both experimentally and mathematically normalizing for shear rate AUC (Figure 6D and E).

The importance of assessing shear rate and then incorporating any differences into the experimental design/analysis is highlighted by the finding that the popliteal artery (PA) exhibited a significantly reduced mean blood velocity profile after 5 minutes of cuff

occlusion when compared to the brachial artery (BA). This, combined with a larger diameter, lead to a much smaller shear rate in the PA compared to the BA (Figure 6A). To experimentally account for this shear rate difference, an additional protocol was performed in which the BA was cuffed for a shorter duration to lessen the ischemic reperfusion response and therefore reduce BA mean blood velocity following cuff release. As a result, shear rates were experimentally matched, and the shear stimulus was thus successfully normalized between the BA and PA (Figure 6C). With this approach the PA appears much more sensitive than the BA to a given shear rate (Figure 6D and E). However, these findings raise the possibility that the BA has a "shear rate threshold" below which a FMD response cannot be elicited. Nevertheless the fundamental aim of these studies was to examine limb-specific shear-mediated vasoreactivity in a scenario in which both the BA and PA received the same shear stimulus, and with this goal achieved the PA responded whereas the BA did not. Therefore, although a simple FMD assessment suggested that the lower extremities tend to have an attenuated vascular function compared to the upper extremities (Figure 6A), when the shear rate stimulus was appropriately incorporated experimentally (Figure 6D) or mathematically (Figure 6E) into the response, the PA of the lower extremities demonstrated greater vascular function than the BA of the upper extremities.

Brachial artery and global vascular health. Although limb-specific vascular responses are gaining recognition (146, 214, 216), it has been commonplace for BA vasodilation (% change) measured by FMD to be used as an index of global vascular health (31, 201). However, the current data reveal that vascular responses to shear stimuli vary significantly across vessels of differing anatomic origin and therefore caution must be exercised when the vascular function of a conduit artery of a single limb is determined and the results translated to systemic vascular health.

Ischemic Reperfusion (IR)

The role of muscle mass. The current data revealed no difference between absolute forearm and lower leg blood flow following cuff-occlusion (Figure 7A). The major dictator of muscle blood flow is metabolism at rest, as in this study, and metabolic demand is predominantly determined by muscle mass (42, 149). Accordingly, it is important to normalize limb blood flow to muscle mass when limbs of differing size are compared. When the large muscle mass differences of the forearm and lower leg were taken into account, blood flow per unit of muscle mass for the lower leg at both rest and following cuff release was significantly attenuated in comparison to the arm. This reveals, for the first time, an inherent difference in resting blood flow and IR between upper and lower extremities (Figure 7B and C).

In addition to the skeletal muscle, other tissue that may promote hyperemia include adipose tissue, fascia, bone, and tendon, but their contributions during IR are, even as a whole, likely minimal (30, 151). Furthermore, skin perfusion, in a normothermic environment, does not significantly correlate with the conduit response during IR (182). Therefore with knowledge of the muscle mass to blood flow relationship, we are left speculating that either the muscle of the leg has a lower metabolic demand, leg muscle exhibits greater O_2 extraction for a given volume of blood, or blood flow itself is directly limited either structurally or functionally and this results in greater O_2 extraction.

Between-limb metabolic heterogeneity. As a result of the integrated metabolic control mechanisms during tissue hypoxia, suprasystolic cuff occlusion creates dilation of downstream resistance vessels and provokes a post-cuff release hyperemia (198, 217). The reduction in substrate delivery and metabolite buildup during occlusion could significantly contribute to this metabolic vasodilation and induce a subsequent fall in downstream resistance (98, 167). Specifically, O_2 demand and debt has long been implicated as a

regulator of blood flow (161, 217). In the current study, cuff occlusion applied to both limbs presents a uniform challenge that results in a reduction in arteriolar Po_2 and the subsequent deoxygenation of hemoglobin during cuff occlusion contributes to vasodilation by stimulating red cell release of NO, or adenosine, prostaglandins, and NO release from the endothelium (51, 66, 120, 155). This progressive deoxygenation was supported in the current study by the intracellular assessment of deoxy-Mb, a marker of resting metabolic rate (161, 163). However, as both the forearm and lower leg revealed the same rate of ischemically-induced Mb desaturation, differences in O_2 consumption do not readily explain the limb

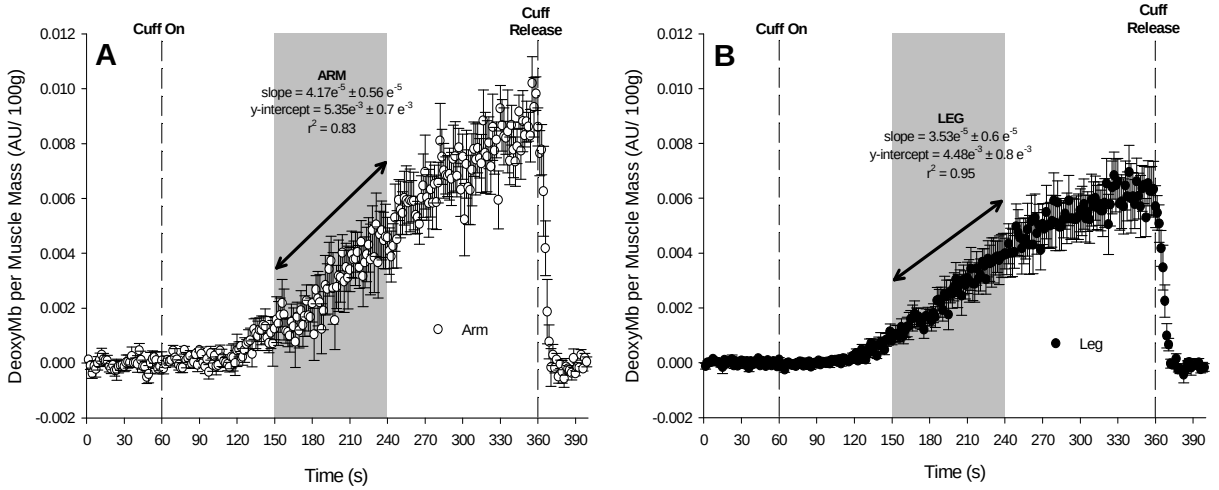


Figure 12. Deoxy-myoglobin kinetics of the forearm (Panel A) and lower leg (Panel B) during cuff occlusion. The data for myoglobin desaturation rate (slope in shaded area) were assessed during the linear portion of the relationship from the point of conclusive myoglobin deoxygenation signal for 90 seconds during cuff-occlusion. AU, arbitrary units.

differences in IR (Figure 12). In fact, they support a similar basal O_2 demand across the skeletal muscle of both the arm and the leg.

In combination, the similar rate of deoxy-Mb signal appearance during cuff occlusion (an index of muscle O_2 consumption) and blood flow per unit of muscle mass collected both at rest and upon cuff release suggest the vascular differences (i.e. elevated blood flow) in the arm when compared to the leg may be a fundamental physiological differences in O_2 extraction. In light of these observations, the Fick equation (O_2 consumption = blood flow ×

(arterial – venous O_2 concentration)) suggests O_2 extraction must be nearly 3 fold different between limbs, with the greater extraction occurring in the leg.

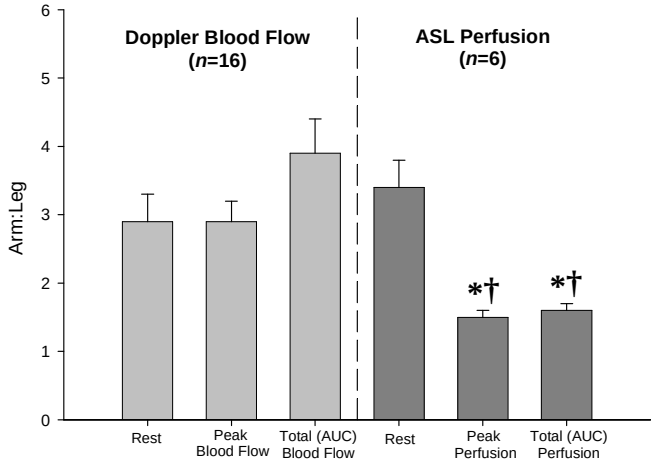


Figure 13. Ratio (fold difference) of arm to leg for rest, peak, and total (AUC) blood flow normalized for muscle mass (Doppler) and perfusion (ASL). * indicates significant difference from rest ($P < 0.05$). † indicates difference between Doppler and ASL ($P < 0.05$). AUC, area under the curve; ASL, arterial spin labeling.

This limb difference was remarkably consistent across scenario (rest and cuff release) and measurement approach (Doppler and ASL). Indeed, the only variance from the approximately 3-fold greater levels in the arm than the leg being the ASL peak and AUC perfusion differences that were less clearly different, but were still significantly greater in the leg (Figure 13). This latter observation may be reconciled by both physiological and sampling heterogeneities in the muscle bed, and remains to be further assessed. This general observation of apparently greater O_2 extraction in the lower leg may be attributed to a greater proportion of oxidative muscle fibers in the leg compared to the forearm (32).

As expected, based upon previous reports (27), PCr hydrolysis in both the forearm and lower leg over the 5 minute cuff occlusion was minimal and revealed no measurable limb-specific metabolic perturbation. In addition, changes in muscle pH have been proposed to alter vascular tone as muscle pH can reduce intracellular Ca^{++} concentration and in turn cause vascular relaxation (141). However, again consistent with previous work in the arm (27), the short ischemic cuff occlusion did not stimulate a change in muscle pH in the muscle

of the arm or leg. Therefore, the difference in limb-specific IR cannot be explained by differential metabolic perturbation, as examined by PCr breakdown or intramuscular pH.

Although there are indeed changes to metabolic factors during cuff occlusion which are known to regulate blood flow (muscle oxygenation and [PCr]), the extent of these changes revealed no significant difference between limbs. Thus, the reduced IR in the leg (Figure 7B and C) suggests that the lower leg may have an attenuated response to these metabolic factors when compared with the forearm. This is in accordance with a previous report by Newcomer *et al.* (128) that found pharmacological and physiological vasodilatory stimuli elicited smaller relative blood flow and vascular conductance changes in the leg than the arm. It is also possible that a blunted responsiveness to vascular stimuli could explain the resting limb differences of a similar magnitude.

Conduit muscle blood flow vs. muscle perfusion. The assessment of local skeletal muscle perfusion with ASL confirmed the contrasting IR exhibited by the forearm and lower leg already documented by Doppler measurements (Figure 7C). Additionally, with the combination of these two modalities, this study offers the unique opportunity to compare and contrast intramuscular hyperemia (ASL) and conduit blood flow (ultrasound Doppler) between limbs (Figure 14). Temporally, conduit vessel blood flow revealed an initial peak within 4-12 seconds in both the forearm and lower leg, in agreement with reports in the literature (134). The temporal response of perfusion was also similar between limbs, with both the forearm and lower leg revealing a consistent initial peak within the time frame of the conduit response, followed by an attenuated flow (most exaggerated in the lower leg), and then a true peak muscle perfusion after ~25-30 seconds (Figure 7C and 14). Reconciling the differences between the reperfusion kinetics in the conduit vessel and the muscle bed is

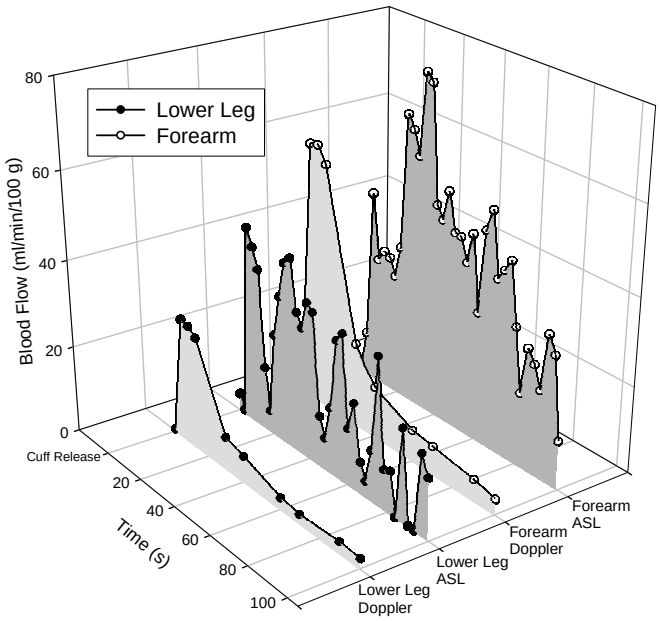


Figure 14. An example of the intramuscular perfusion and conduit blood flow profile in a subject that participated in both Doppler and ASL protocols.

speculative, but perhaps the time delay in intramuscular perfusion could be, in part, explained by the vasodilatory cascade that occurs in the resistance vessels distal to the occlusion upon cuff release (144, 185), which may differ between limbs because of both lower leg structural and functional adaptations. Nonetheless, Figure 14 illustrates typical individual ASL and Doppler data collected from a subject that participated in both protocols and illustrates the similarities/differences between these responses and methods on an individual and group basis (Figure 7B and C), providing at least some initial support for the validity of the current unique observations.

AGING (Papers V and VI)

Structural and Functional Vascular Adaptations with Age.

Over time the human cardiovascular system undergoes many deleterious adaptations, and advancing age has therefore been proposed as a major risk factor for cardiovascular disease (101). Thus, determining the structural and functional vascular alterations with age can help provide mechanistic insight into the age-related increase in vascular disease risk. With the combination of both a structural analysis (IMT) and functional analyses (exercise blood flow,

IR and FMD) this study offers the somewhat unique opportunity to comprehensively evaluate limb-specific peripheral vascular characteristics and the effect of aging.

Structurally, IM thickening with age has been documented in previous studies (81, 135) as in this study (Figure 9). However this work has revealed that aging is accompanied by inherent structural adaptations that are exaggerated in the legs (Figure 9) and although this may not limit blood flow at rest, it may add to the attenuated blood flow response during both exercise (Paper V) and ischemic reperfusion (Paper VI). This aged-related attenuation in blood flow has certainly been well documented, particularly during the challenge of exercise (42, 110). However, it remains to be seen whether the structural changes in the vasculature are truly the cause of a decreased blood flow response with age.

Functionally, advancing age has been typically associated with endothelial dysfunction (17, 205), and a progressive attenuation in nitric oxide synthase (eNOS) expression, impairment of the nitric oxide pathway, and elevated oxidative stress (2, 7, 184, 194). Utilizing the FMD technique, the current data in the BA contradict the dogma of an age-related decline in endothelial function, showing a clear preservation of FMD when normalized to the shear stimulus (Figure 10B). However, the current data reveal that although the PA in the old experienced a similar post-cuff release shear rate to the young, it failed to yield a similar FMD whether or not normalized to the shear stimulus (Figure 10B). In combination, these findings suggest that the vascular dysfunction typically associated with age may be falsely identified in the arm where post-cuff shear rates seem to differ with age, but is clearly present in the leg, and at this site cannot be explained simply by a differing shear stimulus. This dissimilar shear to FMD response in the leg of the elderly group appears to support the concept of a predisposition to vascular dysfunction in the legs, but not the arms, of otherwise healthy older people.

The Effect of Age on Exercising Limb Blood Flow

There were no age-associated differences in exercising forearm blood flow normalized for muscle mass, examined at both absolute and relative exercise intensities (Figure 8A). These findings are qualitatively similar to the only other study that has compared young and old arm blood flow associated with exercise, by Jasperse et al. (88), who documented no difference in postcontraction hyperemia between young and old subjects. In the leg, however, older subjects exhibited a lower leg blood flow than young subjects for a given absolute exercise intensity (Figure 8B). These data are in agreement with the majority of studies that have assessed absolute leg blood flow/vascular conductance during exercise in young and old subjects (10, 110, 145).

In line with the findings of larger aging studies (63), the current subjects were found to have smaller quadriceps muscle mass with increasing age. Acknowledging the relationship between muscle mass and resting blood flow (42, 93), it is tempting to speculate that the smaller quadriceps muscle mass of the old may account for the attenuated exercising blood flow in this study. However, unlike rest, during exercise this would be a vast oversimplification of a complex process based on Henneman's (78) muscle recruitment theory. Specifically, during submaximal exercise, only a portion of the potentially active muscle mass is working (154), and thus at a given absolute work rate, leg blood flow is preferentially distributed to active muscle fibers (5, 106). Therefore, if leg blood flow in the aged population were represented as blood flow per unit muscle mass, this would be an overestimate because each absolute workload for the old subjects represents a greater percentage of their WR_{max} (Figure 8B, *left*). If the aged are working at a greater percentage of their WR_{max}, it is likely that these subjects recruit and perfuse a greater proportion of their quadriceps muscle mass to perform an absolute work rate (5, 106, 154). Consequently, when muscle masses differ between groups of subjects, work rates should be normalized to

percentage of WR_{max} and perfusion should be expressed per unit of muscle mass. When these normalizations were performed on the current data, the older subjects once again revealed an attenuated leg blood flow and vascular conductance at a given percentage of WR_{max} (Figure 8B, *right*).

Vascular Function and Vascular Disease Progression

Several studies have now demonstrated that impaired endothelial function in both the coronary and peripheral circulation precedes the development of pathologies such as atherosclerosis (65, 75, 137, 170). Additionally, in those with atherosclerosis, the lower extremities appears to exhibit both a higher prevalence and a greater degree of impaired endothelial function than the upper extremities (4, 35). Therefore, in both young and old healthy subjects, the study of endothelial function in the upper and lower extremities suggests a greater predisposition and potential progression towards limb-specific vascular dysfunction and therefore susceptibility to vascular disease in these anatomically distinct locations. Indeed, the study of Angerer *et al.* (4) which investigated the effects of coronary artery disease on FMD in the BA and PA, found an attenuated PA FMD when compared to the BA in both patient and age-matched controls (≈ 50 yrs), with the greatest reduction in vascular function in the diseased patients. Unfortunately, this clinical study did not evaluate the shear stimulus, thus limiting accurate inference in the context of the present data. Nevertheless, the current data reveal an intriguing scenario, where both FMD and exercise hyperemia in the arm is preserved with age (Figures 8A and 10B), while the leg reveals a significant age-related attenuation in these variables (Figures 8B and 10B). It is tempting to speculate that the age-related and limb-specific progression of vascular disease described elsewhere (4, 35) is the consequence of physical stresses over the life span which are exclusive to the leg

vasculature, such as larger hydrostatic and transmural forces as well as the continued stresses associated with daily locomotion (53, 115, 171).

SEX DIFFERENCES IN VASCULAR FUNCTION (Paper VII)

A Hormonal Milieu Effect on Flow-Mediated Dilation?

Sex differences in FMD have been reported concomitantly with a greater post cuff hyperemia in nonmenopausal women when compared with age-matched men (112, 175). This effect has been explained by the positive effect of endogenous estrogens on the availability of nitric oxide (NO) (76), the principal vasodilator in shear-mediated vasodilation (125). Indeed, numerous studies have implicated estrogen as both a prostaglandin promoter and an antioxidant (6), protecting NO from degradation, and facilitating increased vasomotion (82, 117, 140). In the present study, female BA relative FMD (% diameter change) was larger than that of the males, a finding that is consistent with the literature in suggesting augmented vascular endothelial-dependent vasodilation in females (figure 11A). However, sex differences in post-cuff release shear rate in the BA, the primary stimulus for endothelial-dependent dilation, were observed in the present study. These findings conform to the stimulus-response paradigm for shear rate and endothelial-dependent vasodilation. Specifically, the lower shear exhibited by the male subjects in the BA elicited a smaller FMD response (figure 11A), however, after normalization for the shear stimulus (AUC), the sex-related difference in both the BA and PA relative FMD was no longer evident (figure 11C). One explanation of the null sex-dependent improvement of vascular reactivity could be the fact that estrogens appear to primarily increase basal release rather than the stimulated NO release (172, 189). Indeed, it was demonstrated that the arterial vasocontrictive effect of NO synthase inhibitors was higher in women that in men despite these same vasodilating effect of acetylcholine between sexes (23, 192). However, although normalized for shear rate this

approach does not compensate for the mathematical bias associated with the smaller starting diameter exhibited by the females. In contrast, in the absolute FMD comparison, the shear rate AUC normalization rendered a similar result in the BA, but revealed a potential a gender difference in the PA. With this approach there is no longer a mathematical bias in favor of the small vessels of the females and may have unveiled a greater vascular sensitivity to shear stress in the lower legs of males.

It must be noted that in the present study, we standardized study visits for women to coincide with days 1–7 of the menstrual cycle, when circulating estrogen is most likely to be lowest and similar to concentrations measured in men (76). Thus, it is likely that the predominant estrogen-mediated mechanisms underlying the present observations in women would have been exerted through the chronic, rather than acute, effects of estrogen on the vasculature. Studies by both Rogers and Sheriff (168) and New *et al.* (127) documented that estrogen significantly modulates vascular regulation independent of female sex. To that end, the study by Hashimoto *et al.* (76) demonstrated that within fluctuations of estrogen levels of the female menstrual cycle, the greatest endothelial-dependent vasodilation, assessed with the cuff-occlusion model, coincided with the end of the follicular phase where serum estradiol levels were highest. In addition, when estradiol levels were similar to concentrations measured in males (i.e. menses), vascular reactivity measured in the BA was similar to that of males. However, the data by Hashimoto *et al.* (76) was not normalized for the shear stimulus. Recognizing the acute effects of estrogen on blood flow regulation (168), it is unknown whether the results of Hashimoto *et al.* (76) may have been affected by an altered reactive hyperemia response at different times of the menstrual cycle. In light of this and the current data, it would be interesting to investigate the normalized FMD in females throughout the menstrual cycle to comprehensively elucidate the acute effects of estrogen on human vascular function. Despite the hypothesis of an increased vasodilation in the BA and/or PA of the

female group, there appears to be no female-specific augmentation of peripheral artery vasodilation. In fact, there is evidence to the contrary with decreased vascular function in the PA of women when absolute FMD is normalized for shear rate AUC.

Vessel Size and Flow-Mediated Dilation.

In general, caution should be exercised when comparing vessels of different sizes as there is a mathematical bias in favor of smaller arteries yielding a larger relative difference. However, in the current limb comparison for both sexes, because the PA has a larger starting diameter than the BA (handicapping % change in the PA), this mathematical bias can not explain the improved vascular responsiveness of the PA in comparison to the BA, but would, in fact, reduce the chance of this observation. Between sexes however, because there are significant

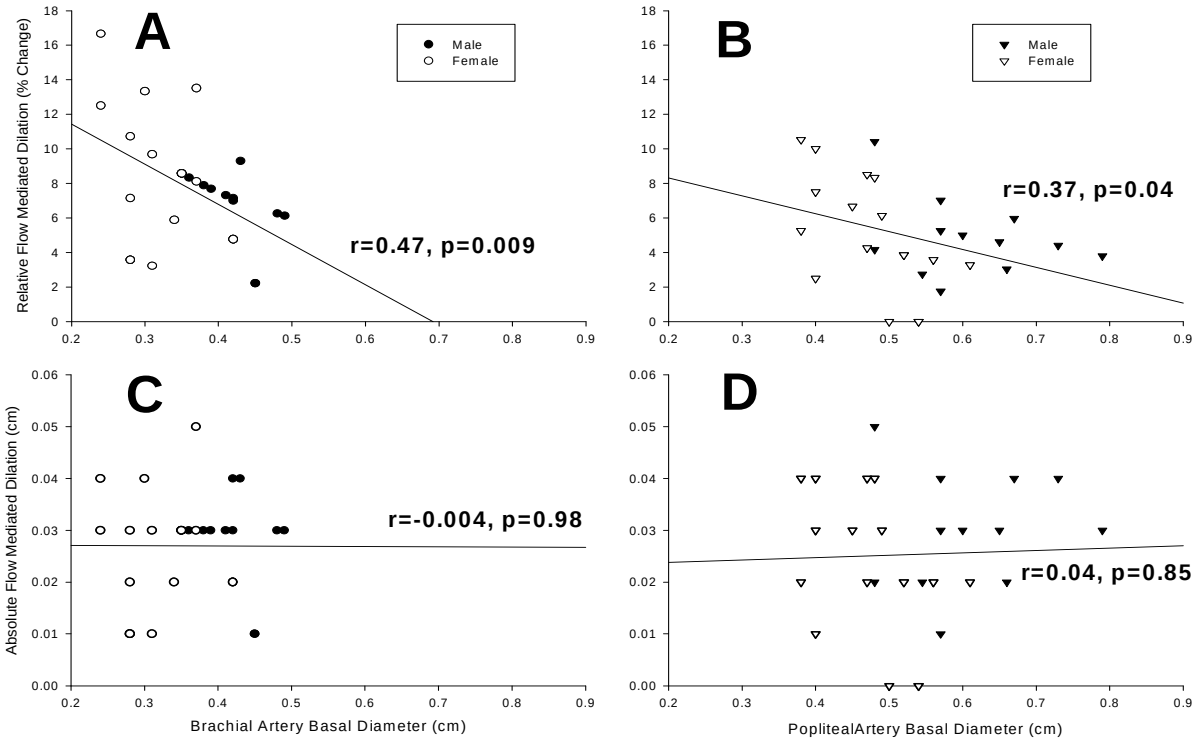


Figure 15. Baseline artery diameter and its influence on relative flow-mediated dilation (% diameter change) (Brachial: Panel A, Popliteal: Panel B) and absolute flow-mediated dilation (Brachial: Panel C, Popliteal: Panel D).

differences in starting diameters between males and females for the BA and PA, definitive conclusions cannot be drawn from the relative diameter changes data. In the present study, as in other studies (21, 89, 102, 127), the flow-induced change in artery diameter is inversely related to the basal value of the diameter when expressed in percent change from baseline (relative FMD) in both the BA and PA (figure 15A and 15B). This supports the idea that larger arteries show a less convincing relative vasodilation compared to smaller arteries. Correlation analyses of the flow-induced change in artery diameter expressed as an absolute change from basal diameter reveals no such relationship (figure 15C and 15D). This supports the latter analytical approach as the most unbiased interpretation when considering vessels of different size. Thus, definitive statements concerning differences in endothelial function between the sexes need to be carefully interpreted if compared solely in relative terms.

CONCLUSIONS

Inherent limb differences appear to exist, and to different extents in varied populations. These studies have elucidated several underlying mechanisms defining vascular heterogeneities, all of which are important for understanding skeletal muscle blood flow and vascular control mechanisms in not only a healthy population, but also in diseased populations that may to exhibit limb-specific vascular dysfunction.

I. This study demonstrates that the brachial artery of healthy subjects vasodilates less following the ingestion of an antioxidant cocktail during submaximal exercise, despite similar or slightly elevated shear rates. This suggests that an antioxidant-induced reduction in oxidative stress, as supported by blood EPR measurements, negatively impacts the natural balance between pro- and antioxidant forces that exists in normal healthy subjects. This reveals a reliance on free radical-mediated vasodilation, most likely induced by the increased oxidative stress of exercise per se (increased metabolic rate) or the shear-induced release of free radicals by the vascular endothelium.

II. This study reveals that sympathetically-mediated vasoconstriction in response to the CPT at rest is not limb-specific or affected by exercise training status, and that acute exercise effectively blunts sympathetic vasoconstriction (i.e. sympatholysis) in both trained and untrained limbs. However, there was a reduced magnitude of sympatholysis in the arm of predominantly leg-trained individuals, exemplifying the systemic vascular effects of exercise training that may optimize blood flow distribution to meet limb-specific demand.

III. This study highlights the importance of both quantifying and accounting for the shear stimulus in FMD studies. Without either experimental or mathematical normalization of this important variable, clear limb-specific differences in endothelium-dependent vasoreactivity would not have been unveiled. With this approach, the present data suggest that the PA in a healthy, young, male population exhibits an enhanced vascular response to a given shear stimulus when contrasted with the BA.

IV. There is a clear and robust difference in skeletal muscle blood flow between limbs that is maintained from rest to IR. Although the exact mechanism for this limb-specific difference has not been completely determined, many potential mechanisms have been excluded, leading to the conclusion that observed responses may be due in part to difference in O_2 extraction between the skeletal muscle of the arm and leg. However, it is still unclear whether this differing O_2 extraction paradigm is the consequence or cause of the limb-specific difference in the control of skeletal muscle blood flow.

V. During single-leg knee extensor exercise, older subjects exhibit a reduced leg blood flow that was still evident when differences in muscle recruitment were taken into account. In contrast, arm blood flow during forearm exercise is not influenced by age and was not complicated by differences in work rate. Therefore, age-associated changes in blood flow during exercise are not uniform across limbs.

VI. The structural analysis of vascular IMT across limbs revealed an age-related thickening of peripheral conduit arteries that is more pronounced in the legs. FMD data reveal that the brachial artery of older healthy subjects exhibits a preserved endothelial-dependent vascular reactivity when shear is taken into account. In contrast, this does not appear to

be the case in the popliteal artery and, in combination with structural alterations, may be indicative of a limb-specific and age-related progression towards vascular dysfunction in the legs that precedes clinical signs of vascular disease.

VII. The present investigation extends previous findings in young, healthy males of greater endothelial-dependent vascular reactivity in the lower compared to the upper extremities to females. It is also concluded that basal vessel diameter and shear rates influence the magnitude of relative flow-mediated vasodilation and that the sex differences previously reported could be the consequence of a mathematical bias and differences in shear stimulus rather than a sex-related physiological difference. These vascular characteristics are essential to the appropriate interpretation and thus should be taken into account when comparing the vascular responsiveness of men and women. Therefore, when the most rigorous analysis for these conditions, absolute FMD normalized for shear rate, is applied the BA does not exhibit a difference between the sexes, whereas, the PA displays attenuated function in females.

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50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

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52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.

70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

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74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.

111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.

142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.

174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS

203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING

231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
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