Oxygen Consumption in the Heart, Hepatomesenteric Bed, and Brain in Young and Elderly Human Subjects, and Accompanying Sympathetic Nervous Activity

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Although the reduction in whole-body energy expenditure with aging has been well documented, there is little information about the changes that individual organs undergo. We therefore measured oxygen consumption in the heart, hepatomesenteric bed, and brain in elderly subjects and young controls, using central venous catheter techniques and the application of Fick's principle. We also measured whole-body, cardiac, and hepatomesenteric sympathetic nervous activity using isotope dilution methodology. Cardiac, hepatomesenteric, and cerebral oxygen consumption was similar in both groups. Whole-body and hepatomesenteric sympathetic nervous activity was also similar in the study groups, whereas cardiac norepinephrine (NE) spillover was significantly higher in the elderly. In contrast to the young, cardiac sympathetic nervous activity as assessed from NE spillover was not related to either cardiac oxygen consumption or cardiac work in the elderly. The data suggest that although oxygen consumption in the heart, hepatomesenteric bed, and brain are not different between young and elderly individuals, the relationship between sympathetic nervous activity and oxygen consumption in individual organs may alter with aging.

THE REDUCTION in whole-body energy expenditure with aging has been the subject of considerable research both in the past (reviewed in Poehlman and Horton[1]) and in more recent investigations.[2-6] In contrast, there is little information about the possible age-related changes that individual organs undergo with respect to energy expenditure. Some attempt has been made to characterize the role of skeletal muscle.[7] However, despite its large mass, skeletal muscle contributes only between 15% and 30% of the resting metabolic rate in the healthy adult.[8-10] Given that structural and functional changes with increasing age encompass a whole range of organ systems,[11] it is conceivable that changes in energy expenditure may occur in multiple organs. The brain, liver, and heart are among the organs that show signs of senescence, and although they are of small mass, they are highly metabolically active, being collectively responsible for approximately half the resting oxygen consumption in the healthy adult (brain, ~19%; liver, ~27%; and heart, ~7%).[9] In this study, we used central venous catheter techniques to investigate whether there are age-related differences in brain, hepatomesenteric, and cardiac oxygen consumption, by studying a group of young healthy adult males (18 to 30 years) and comparing them with a group of elderly males (>60 years).

The sympathetic nervous system is an important determinant of energy expenditure,[12] and increasing age is known to alter plasma norepinephrine (NE) kinetics.[13-16] Since sympathetic nervous activity can vary between organs,[17] we assessed both whole-body and regional sympathetic nervous activity of the heart and hepatomesenteric bed using isotope dilution methodology.[18]

SUBJECTS AND METHODS

Subjects

Twenty-one healthy adult male subjects were recruited for the study after provision of written consent to the protocol, which was approved by the Ethics Review Committee of the Alfred Hospital. All subjects had a detailed clinical evaluation that included a medical history, clinical examination, and routine hematology and biochemistry. None were receiving medications. The volunteers were divided into a young group (n = 9) and an elderly group (n = 12). Characteristics of the subjects are summarized in Table 1.

General Procedure

The experiments were performed in the morning as an outpatient procedure in an experimental room maintained at an ambient temperature between 21°C and 23°C, following a 12-hour abstinence from alcohol, nicotine, and caffeinated beverages. On the morning of the study, all subjects had a standard light breakfast consisting of a single slice of toast with thinly spread margarine, cereal, and milk (345 kcal). It is our experience that consumption of a light breakfast reduces the chance of vasovagal syncope during the procedure. We have previously demonstrated that consumption of a much larger meal (~700 kcal) does not increase oxygen consumption in the heart, and increases oxygen consumption only minimally across the hepatomesenteric bed.[19] Postprandial sympathetic nervous activation following a moderately sized mixed meal is seen predominantly in skeletal muscle and the renal vascular bed.[19,20]

Blood samples were obtained from a central venous and arterial catheter inserted percutaneously under local anesthesia. Central venous catheter placement was performed via an 8.5F percutaneous introducing sheath (Arrow International, Reading, PA) inserted into the antecubital vein of the forearm, and a 7F type CCS-7U coronary sinus thermodilution catheter (Webster Laboratories, Baldwin Park, CA). The catheter was guided fluoroscopically (model DC 12MB-1; Toshiba Industries, Osaka, Japan), and the position of the catheter tip was confirmed with the injection of 2

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Table 1. Subject Characteristics

Characteristic	Young (n = 9)	Elderly (n = 12)	*P*
Age (yr)	22 ± 1	65 ± 4	.000
Height (cm)	181.1 ± 1.6	174.0 ± 1.7	.011
Weight (kg)	74.8 ± 3.9	78.7 ± 2.5	.176
BMI	22.8 ± 1.1	26.0 ± 0.8	.023
Heart rate (bpm)	58 ± 4	66 ± 3	.08
Systolic BP (mm Hg)	131 ± 2	138 ± 4	.21
Diastolic BP (mm Hg)	69 ± 1	66 ± 3	.185

NOTE. Results are the mean ± SEM. Intergroup comparisons were made using the Mann-Whitney test.

Abbreviation: BP, blood pressure.

mL radio-opaque contrast medium (Omnipaque; Winthrop Pharmaceuticals, New York, NY). Venous blood samples were obtained from one or more of several sites, including the right or left internal jugular vein (young, n = 6; elderly, n = 6), coronary sinus (young, n = 7; elderly, n = 11), and hepatic vein (young, n = 7; elderly, n = 8). As in previous studies in which we have used multiple-site central venous sampling for measurement of regional noradrenaline kinetics and oxygen consumption, 5 to 10 minutes was allowed for stabilization after each of these catheter placements. We have recently provided evidence that catheter repositioning does not constitute a material stressor, in experienced hands.[19] Jugular and coronary sinus blood flow was obtained by thermodilution, and hepatic plasma flow from the clearance of indocyanine green, as in our previous studies.[21-23] Simultaneous arterial blood samples were obtained from a 21G cannula inserted into either the radial or brachial artery.

Throughout the course of the experiment, a tracer infusion of ^{3}H-labeled L-NE (specific activity, 11 to 25 Ci/mmol; New England Nuclear, Boston, MA) was administered intravenously at 0.8 μCi/min via a dorsal vein in the hand.

Biochemical Analysis

Blood samples for the estimation of catecholamines were transferred immediately to ice-chilled tubes containing EGTA and reduced glutathione and then centrifuged at 4°C, and the plasma was stored at −70°C before assay. Plasma NE concentration was determined by high-performance liquid chromatography with electrochemical detection. Timed collection of the eluate leaving the detection cell using a fraction collector permitted separation of ^{3}H-labeled NE for counting by liquid-scintillation spectroscopy. Intraassay variations were 4.5% for plasma NE at a concentration of 140 pg/mL and 7.2% for ^{3}H-labeled NE.

Blood samples for blood gases were collected in heparinized syringes. Hemoglobin oxygen saturation was measured using an OSM2 Hemoximeter (Radiometer, Copenhagen, Denmark), and po_2 was measured using an ABL 500 Blood Gas Machine (Radiometer).

Calculations

Whole-body plasma NE clearance and spillover were calculated using the following formulae: (1) plasma NE clearance = ^{3}H-labeled NE infusion rate (dpm/min)/plasma ^{3}H-labeled NE concentration (dpm/mL), and (2) NE spillover = ^{3}H-labeled NE infusion rate (dpm/min)/plasma NE specific activity (dpm/pg).

Regional NE spillover was calculated using the equation, $[(NE_v - NE_a) + (NE_a \cdot NE_{ex})] \cdot$ plasma flow, where NE_a and NE_v are the arterial and venous concentrations of NE and NE_{ex} is the fractional extraction of tracer NE across the organ.

Regional oxygen consumption was calculated as in earlier studies[19,24] from arteriovenous differences in oxygen content and the regional blood flow, using Fick's principle. Oxygen content of the blood (milliliters per deciliter) was calculated as (Hb × saturation % × 1.34) + (po_2 × 0.003), where Hb is hemoglobin concentration, 1.34 is the stoichiometric oxygen-binding capacity of the hemoglobin molecule (Hufner's number), and 0.003 is the solubility factor for oxygen.

Cardiac oxygen consumption was normalized for cardiac mass, with left ventricular mass determined by M-mode echocardiography using the equation of Devereux et al.[25] This is based on measures of left ventricular internal dimension and interventricular septal and posterior wall thickness.

Statistical Analysis

All results are expressed as the mean ± SEM. Because of the small sample size, data were analyzed nonparametrically using the Mann-Whitney test for intergroup comparisons. Spearman's rank correlation coefficients (R_s) were used to determine whether associations between sympathetic nervous and metabolic activity existed for the various organs, within each group. The significance of Spearman's correlation coefficients was calculated from standard tables.[26] The null hypothesis was rejected at P less than .05. The data were analyzed using SYSTAT for Macintosh, version 5.2 (Evanston, IL).

RESULTS

Elderly subjects had significantly lower hemoglobin concentrations (young, 14.9 ± 0.4; elderly, 13.6 ± 0.3 g/dL, $P < .05$) and hematocrit levels (young, 0.44 ± 0.01; elderly, 0.41 ± 0.01, $P < .05$) than their younger counterparts. This, in combination with the generally lower arterial oxygen saturation and arterial pO_2 values in the elderly, translated into a significantly lower oxygen content in arterial blood in the elderly (Table 2). Hepatic and internal jugular blood flows were not different in the young and elderly. This resulted in a nonsignificantly higher oxygen delivery in the young of 24% to the hepatomesenteric bed (young, 232.0 ± 30.7; elderly, 187.3 ± 13.1 mL O_2/min, $P = .355$) and 23% to the brain (young, 63.0 ± 10.0; elderly, 51.3 ± 9.6 mL O_2/min, $P = .522$). In the heart, the 12% higher coronary sinus blood flow in the elderly maintained oxygen delivery at comparable levels in both groups (young, 31.9 ± 4.0; elderly, 32.2 ± 3.1 mL O_2/min, $P = .964$). The venous oxygen content was significantly lower in all vascular beds in the elderly, and although percent oxygen extraction was generally higher in the elderly, this did not achieve statistical significance with our sample size (hepatomesenteric, $P = .064$; cardiac, $P = .094$; cerebral, $P = .262$). Oxygen consumption was similar in both study groups across all vascular beds (Fig 1).

In the case of the heart, quantification of left ventricular mass allowed for the determination of metabolic activity per unit tissue mass. Left ventricular mass was similar in both groups (young, 173.8 ± 12.7; elderly, 157.8 ± 13.8 g). Cardiac oxygen consumption expressed per unit cardiac muscle was also similar in the two study groups (young, 0.12 ± 0.02; elderly, 0.14 ± 0.02 mL/g/min). To account for differences in heart rate, cardiac oxygen consumption was also expressed per heart beat. This was again not significantly different between the two groups (young, 0.3 ± 0.04; elderly, 0.3 ± 0.03 mL/beat). The thermodynamic efficiency of external cardiac work[27] expressed in

Table 2. Regional Metabolic Characteristics of the Two Study Groups

	No. of Subjects	Arterial O_2 Saturation (%)	Arterial pO_2 (mm Hg)	Arterial O_2 Content (mL/100 mL)	Venous O_2 Content (mL/100 mL)	Blood Flow (mL/min)	Oxygen Consumption (mL/min)
Hepatomesenteric							
Young	7	98.0 ± 0.2	100.8 ± 1.5†	19.8 ± 0.6*	15.4 ± 0.5*	1,189 ± 184	52.2 ± 9.7
Elderly	8	97.3 ± 0.4	90.5 ± 2.3	17.7 ± 0.4	12.8 ± 0.5	1,064 ± 87	52.2 ± 4.9
Cardiac							
Young	7	97.6 ± 0.2†	103.3 ± 2.7†	19.8 ± 0.6*	7.5 ± 0.6*	161 ± 19	19.9 ± 2.6
Elderly	11	96.2 ± 0.4	83.7 ± 2.6	17.8 ± 0.4	5.7 ± 0.4	181 ± 18	21.4 ± 1.9
Cerebral‡							
Young	6	97.9 ± 0.2*	103.8 ± 3.5†	20.2 ± 0.5†	14.8 ± 0.5†	315 ± 52	17.1 ± 3.3
Elderly	6	96.8 ± 0.3	87.1 ± 3.2	17.9 ± 0.2	12.2 ± 0.3	289 ± 56	16.5 ± 3.4

NOTE. Results are the mean ± SEM. Intergroup comparisons were made using the Mann-Whitney test.

*$P < .05$.

†$P < .01$.

‡Total cerebral oxygen consumption would be approximately twice the values cited, when allowing for extraction across the contralateral internal jugular vein.

arbitrary units, calculated as the rate-pressure product divided by cardiac oxygen consumption, was also similar in both groups (young, 437 ± 81; elderly, 482 ± 78).

Table 3 summarizes whole-body, cardiac, and hepatomesenteric spillover of plasma NE in the two study groups. Arterial plasma NE levels were 50% higher in the elderly compared with the young ($P < .05$). This reflected a reduction in the plasma clearance of NE in the elderly of approximately 20% ($P = .065$). The whole-body spillover of NE to plasma was 20% higher in the elderly, although this was not statistically significant. Hepatomesenteric spillover of NE was also similar in the two study groups, accounting for 9.3% and 6.8% of whole-body NE spillover in the young and elderly, respectively.

Extraction of tracer NE across the heart was significantly lower in the elderly, who also exhibited a significantly higher cardiac spillover of NE. Cardiac NE spillover in the elderly accounted for 4.1% of whole-body NE spillover, whereas the corresponding figure in the young was 2.2% ($P < .02$). In the young, cardiac oxygen consumption was significantly related to the double product, a surrogate for the external work of the heart (Spearman's rank correlation coefficient (R_s) = .929, $P < .01$). In the same group, cardiac NE spillover was significantly related to the cardiac oxygen consumption and the double product (both R_s = .929, $P < .01$). In contrast, there was no linear relationship between cardiac oxygen consumption and the double product in the elderly (R_s = .2). Cardiac NE spillover was also unrelated to the cardiac oxygen consumption and double product in the elderly (R_s = .573 and .255, respectively). This is depicted in Fig 2.

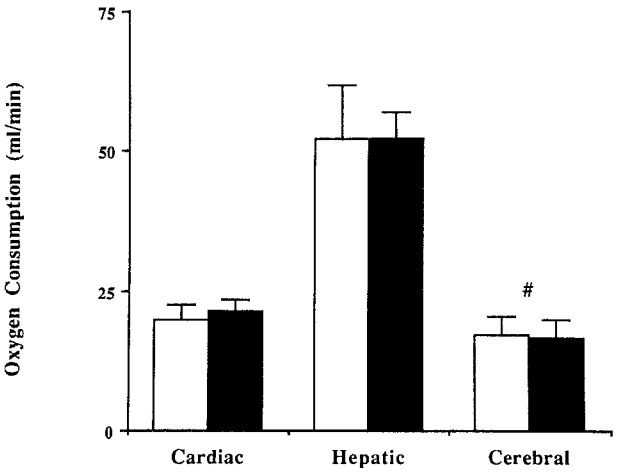

Fig 1. Comparison of oxygen consumption in the heart, hepatomesenteric bed, and brain in young (□) and elderly (■) subjects. There were no significant differences. #Cerebral oxygen consumption depicted in the figure is derived from unilateral internal jugular vein sampling. Total cerebral oxygen consumption would be approximately twice this.

DISCUSSION

There is substantial evidence in the literature on the basis of which we would have expected age-related changes in oxygen consumption of the heart, hepatomesenteric bed, and brain. The cardiovascular changes with aging have been reviewed recently.[28] Aging is associated with a progressive loss of myocytes[29] and an increase in the rate of degenerative changes such as lipid deposition, tubular dilation, and lipofuscin deposition.[29,30] In addition, the elderly may also have diastolic dysfunction with increased relaxation times.[31]

Table 3. Comparison of Whole-Body and Regional Sympathetic Nervous Activity in Young and Elderly Subjects

Activity	Young	Elderly	*P*
Whole-body			
Sample (n)	9	12	
Arterial plasma NE (pg/mL)	181 ± 19	271 ± 26	.023
NE clearance (mL/min)	3,294 ± 330	2,588 ± 226	.065
Plasma NE spillover (ng/min)	622 ± 67	752 ± 153	.972
Hepatomesenteric			
Sample (n)	7	8	
Extraction of ^{3}H-NE	0.98 ± 0.01	0.96 ± 0.01	.28
NE spillover (ng/min)	58.0 ± 24.6	51.1 ± 13.8	.643
Cardiac			
Sample (n)	7	11	
Extraction of ^{3}H-NE	0.86 ± 0.03	0.73 ± 0.05	.029
NE spillover (ng/min)	13.9 ± 2.6	30.1 ± 4.0	.006

NOTE. Results are the mean ± SEM. Intergroup comparisons were made using the Mann-Whitney test.

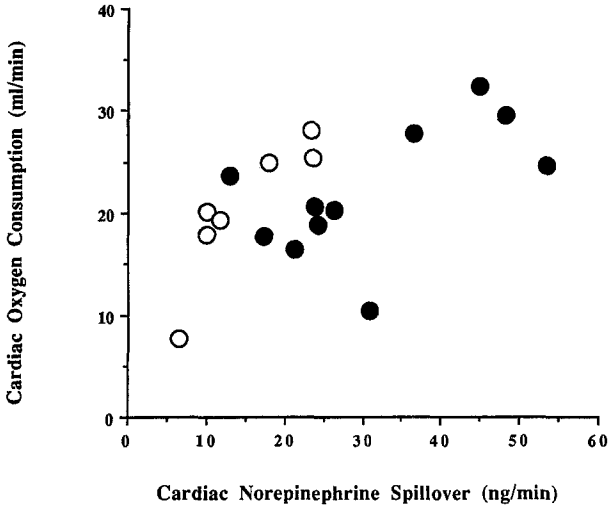

Fig 2. Comparison of cardiac NE spillover and oxygen consumption in young (○) and elderly (●) subjects. There was no relationship between NE spillover and oxygen consumption in the elderly.

This is important, since myocardial relaxation requires more oxygen and energy than does contraction, as indicated by studies that have shown that relaxation is more vulnerable to hypoxia and ischemia.[32] In the liver, aging is associated with a decrease in liver volume[33] and a reduction in function, indicated in a variety of tests including hepatic nitrogen clearance,[33] galactose elimination capacity,[34,35] caffeine clearance, and the ^{14}C-aminopyrine breath test.[35] Goldman, et al,[36] in a recent review, summarized several studies that have demonstrated both neuronal loss and neuronal atrophy with aging. These structural changes would be expected to have important functional consequences, including those related to local oxygen utilization.

In addition to the changes already outlined, all the vascular beds we studied show age-related increases in mitochondrial damage (for review, see Beal[37]). This clearly has implications for oxidative phosphorylation, energy metabolism, and oxygen consumption. Despite this evidence, we were unable to demonstrate any differences in oxygen consumption across the heart, hepatomesenteric bed, and brain in the elderly compared with the young controls. In the heart, oxygen consumption per unit tissue mass was similar in the young and elderly groups. This is in accordance with whole-body data, reviewed recently,[1] which suggest that there is no important difference in the metabolic activity of body cell mass per se between younger and older individuals. A significant reduction in the arterial oxygen content in the elderly, described previously[38] and confirmed in the present study, clearly did not limit oxygen consumption at rest. However, it is conceivable that this may have implications under conditions of stress with the accompanying enhanced metabolic demand.[39]

The elderly in this study had 50% higher resting arterial plasma NE levels compared with the young, in accordance with several other studies.[15,16,40,41] Studies in the past that have used the isotope dilution technique of assessing sympathetic nervous activity have demonstrated that older individuals have both an increased rate of spillover of NE into plasma[14,41,42] and a lower clearance from it.[13,16] The increased NE spillover and reduced extraction of tracer NE across the heart in the elderly is in accordance with our previous studies.[40] The increased cardiac NE spillover in the elderly has been attributed at least in part to the reduced neuronal reuptake of the neurotransmitter.[40] The elderly in the present study had a significantly higher body mass index (BMI) than the young subjects, so it is difficult to discriminate between the effects on cardiac sympathetic nervous function attributable to aging and those attributable to differences in body composition. In an earlier study,[16] we did observe cardiac NE spillover to be significantly elevated in the elderly in BMI-matched younger and older subjects, much as in the present case, but even with BMI matching in the earlier experiment body fat mass would have differed.

In addition, the present data demonstrate that certain relationships between cardiac sympathetic nervous activity and cardiac oxygen consumption demonstrable in the young are lost with aging. The rate-pressure product (double product), a commonly used index of cardiac external work, was related to cardiac oxygen consumption in the young but not in the old. Despite a greater than twofold increase in cardiac sympathetic nervous activity in the elderly, cardiac oxygen consumption was similar to that in the young. This would be plausible if there were a blunting of tissue responses to the enhanced sympathetic nervous activation. There is in fact evidence for a diminution of myocardial β_1-adrenergic receptors,[43] as well as a reduction in adrenergic responsiveness, with aging.[43,44] The absence of associations between cardiac sympathetic nervous activity and cardiac oxygen consumption in the elderly suggests that the elderly are a more heterogenous group than the young.[28] Life-style and environment may be important determinants of the rate, extent, and functional consequences of processes that are attributable to aging.

Limitations of the Study

In this study, we did not measure whole-body oxygen consumption. We decided not to incorporate these measurements into the cardiac catheter laboratory procedure due to the existing complexity of the catheter procedure, and chose not to make these measurements on a second day because of doubts that they would be adequately representative of events during the invasive procedure. We are therefore unable to comment on the relative contributions of the organs we studied to whole-body oxygen consumption in the two groups.

We determined cerebral oxygen consumption from arteriovenous oxygen differences across the jugular vein. Brain oxygen consumption would be approximately twice the values depicted in Table 2, ie, on the order of 34 mL/min. Our determination of brain oxygen consumption using this extrapolation is lower than in earlier reported studies.[45] This may be explained partly by the difference in methodology used to estimate cerebral blood flow, with our thermodilution-derived estimate being approximately 17% lower than that derived using the nitrous oxide method.[45] Part of

the underestimation is related to the fact that approximately 5% of cerebral blood drainage occurring via the external jugular veins[46] is not accounted for by our method. In addition, the extrapolation to total brain oxygen consumption in our study assumes that there are no differences in either blood flow or oxygen extraction in the contralateral internal jugular vein. However, our data do not exclude the possibility of age-related changes in both blood flow and oxygen consumption in smaller discrete areas of the brain. ^{133}Xe-inhalation studies have in fact provided evidence that aging is associated with reductions in blood flow in discrete areas of the brain.[47] Similarly, a diminished oxygen consumption in several regions of the brain has been demonstrated using the oxygen 15 continuous-inhalation technique and PET.[48]

In this study, no attempt was made to relate cerebral oxygen consumption to the jugular NE spillover. This was because jugular NE spillover gives an incomplete measure of brain NE turnover, due to the presence of a partial brain-blood barrier for the catecholamine.[49] Further, the activity of discrete noradrenergic nuclei in the brain would not be related to more global phenomena such as cerebral oxygen consumption. We also refrained from relating oxygen consumption and NE spillover in the hepatomesenteric bed. This would have been simplistic, given the complexity of the splanchnic circulation with its portal circulation. Almost all NE released from the gut to the plasma is removed in transit through the liver.[50] Separation of liver and mesenteric effects would have allowed for more detailed comparisons. This has been achieved in instrumented animals,[50] but it clearly remains a limitation in human studies.

In conclusion, the data suggest that while cardiac, hepatomesenteric, and cerebral oxygen consumption are not different in young and elderly individuals, the relationship between sympathetic nervous activity and oxygen consumption in individual organs such as the heart may alter with aging.

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