

# Impact of Aging on Substrate Metabolism by the Human Heart

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<b>BACKGROUND</b>	Results of studies in experimental animals have shown that, with age, myocardial fatty acid metabolism decreases, and glucose metabolism increases. Whether similar changes occur in humans is unknown.
<b>METHODS</b>	Seventeen healthy younger normal volunteers (six males, $26 \pm 5$ years) and 19 healthy older volunteers (nine males, $67 \pm 5$ years) underwent positron emission tomography (PET) under resting conditions in the fasted state. Myocardial blood flow (MBF), myocardial oxygen consumption ( $MVO_2$ ), myocardial fatty acid utilization (MFAU) and oxidation (MFAO), and myocardial glucose utilization (MGU) were quantified by PET with $^{15}O$ -water, $^{11}C$ -acetate, $^{11}C$ -palmitate, and $^{11}C$ -glucose, respectively.
<b>RESULTS</b>	Although MBF was similar between the groups, $MVO_2$ was higher in the older subjects ( $5.6 \pm 1.6 \mu\text{mol/g/min}$ ) compared with younger subjects ( $4.6 \pm 1.0 \mu\text{mol/g/min}$ , $p < 0.04$ ). Rates of MFAU and MFAO (corrected for $MVO_2$ ) were significantly lower in older subjects than in younger subjects (MFAU/ $MVO_2$ : $35 \pm 10$ vs. $51 \pm 20$ nmol free fatty acids (FFA)/nmol $O_2 \times 10^{-3}$ , $p < 0.005$ , and MFAO/ $MVO_2$ : $33 \pm 10$ vs. $48 \pm 18$ nmol FFA/nmol $O_2 \times 10^{-3}$ , $p < 0.004$ ). In contrast, the rates of MGU corrected for $MVO_2$ did not differ between the groups.
<b>CONCLUSIONS</b>	With aging, humans exhibit a decline in MFAU and MFAO. Although absolute rates of MGU do not increase, by virtue of the decline in MFAU there is likely an increase in relative contribution of MGU to substrate metabolism. The clinical significance of this metabolic switch awaits further study. (J Am Coll Cardiol 2003;41:293-9) © 2003 by the American College of Cardiology Foundation

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Cardiovascular disease is a primary cause of disability and death in Americans 65 years of age or older (1,2). Aging is associated with a variety of cardiac abnormalities. For example, there is an age-related decline in myocardial vasodilator capacity (3,4). Although ventricular systolic function at rest is preserved, both left ventricular systolic reserve capacity and diastolic filling decline with age (5). In addition to these normal aging effects on myocardial perfusion and function, both the incidence and clinical manifestations of a variety of cardiac disorders such as dilated cardiomyopathy, hypertension-induced left ventricular hypertrophy, and cardiomyopathy associated with diabetes mellitus increase with age (5-7). Numerous mechanisms, such as tissue oxygen free-radicals and reduced  $\beta$ -adrenergic sensitivity, have been proposed for being at least partially responsible for these age-related effects on the heart (8-10).

However, alterations in the pattern of myocardial substrate use may play a key role as well. Based on results of studies in experimental animals, the pattern of myocardial substrate metabolism varies with advancing age. In the mature heart, fatty acids are the preferred energy source

(11,12). With senescence, there is a decline in fatty acid metabolism, and the proportion of glucose metabolism to overall substrate metabolism increases (13,14). Whether similar age-related changes in myocardial substrate metabolism occur in humans is unknown. Accordingly, the purpose of the current study was to determine if there is an age-related shift in myocardial substrate metabolism in healthy older humans.

## METHODS

**Study population.** Seventeen young, sedentary, healthy subjects (six men; mean age,  $26 \pm 5$  years) and 19 older, sedentary, healthy subjects (nine men; mean age,  $67 \pm 5$  years) were studied. Sedentary subjects were chosen to minimize the confounding effects of variable levels in training-induced adaptations of myocardial substrate metabolism. All subjects were nonsmokers, normotensive, and were without a family history for coronary artery disease. Occult diabetes was excluded by an oral glucose tolerance test, although two of the older subjects had evidence of borderline glucose intolerance. Hyperlipidemia was excluded by a normal plasma lipid profile. None of the subjects had any other systemic illness. No subjects were taking any medications at the time of the study. Subclinical coronary artery disease and other forms of cardiac disease were excluded by a normal physical exam and a normal rest/exercise echocardiogram. Normal left ventricular systolic

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**Abbreviations and Acronyms**

FFA	= free fatty acids
GLUT-4	= glucose transporter isoform 4
MBF	= myocardial blood flow
MFAO	= myocardial fatty acid oxidation
MFAU	= myocardial fatty acid utilization
MGU	= myocardial glucose utilization
MVO <sub>2</sub>	= myocardial oxygen consumption
PET	= positron emission tomography

function at rest was confirmed by demonstration of a normal left ventricular ejection fraction in both the younger ( $65 \pm 7\%$ ) and older subjects ( $68 \pm 5\%$ ,  $p = \text{NS}$ ) quantified on the echocardiograms. Left ventricular hypertrophy was excluded by confirming with echocardiography a normal left ventricular mass index in both the younger ( $79 \pm 9 \text{ g/m}^2$ ) and older ( $76 \pm 10 \text{ g/m}^2$ ,  $p = \text{NS}$ ) groups. The study was approved by the Human Studies and the Radioactive Drug Research Committees at the Washington University School of Medicine. Written informed consent was obtained from all subjects before enrollment into the study.

**Imaging protocol.** All studies were performed on a conventional commercially available tomograph (Siemens ECAT 962 HR+, Siemens Medical Systems, Iselin, New Jersey). All subjects were studied after an overnight fast under resting conditions. They were placed on telemetry and had blood pressures obtained routinely throughout the study. Positron emission tomography (PET) was used to measure myocardial blood flow (MBF) with <sup>15</sup>O-water, myocardial oxygen consumption (MVO<sub>2</sub>) with <sup>11</sup>C-acetate, myocardial fatty acid utilization (MFAU) and oxidation (MFAO) with <sup>11</sup>C-palmitate, and myocardial glucose utilization (MGU) with <sup>11</sup>C-glucose. During the study, venous blood samples were obtained at predetermined intervals to measure plasma substrate (glucose, fatty acids, and lactate) and insulin levels. In addition, plasma levels of <sup>11</sup>CO<sub>2</sub> values and <sup>11</sup>C-lactate were measured to correct the arterial input function during compartmental modeling of the myocardial kinetics of the various metabolic tracers (see the following text).

**Image analysis.** Myocardial <sup>15</sup>O-water, <sup>11</sup>C-acetate, <sup>11</sup>C-glucose, and <sup>11</sup>C-palmitate images were generated and then reoriented to standard short- and long-axis views. To generate myocardial time-activity curves, regions of interest encompassing the anterior-lateral wall (3 to 5 cm<sup>3</sup>) were placed on three to four midventricular short-axis slices of composite <sup>15</sup>O-water, <sup>11</sup>C-acetate, <sup>11</sup>C-glucose, and <sup>11</sup>C-palmitate images as previously described (15). To generate blood time-activity curves for each tracer, a small region of interest (1 cm<sup>3</sup>) was placed within the left atrial cavity on a midventricular slice in the horizontal long-axis orientation of each composite image. Within these regions of interest, myocardial and blood time-activity curves were generated for each of the tracer data sets. Subsequently, blood and myocardial time-activity curves were used in conjunction

with well-established kinetic models to measure MBF, MVO<sub>2</sub>, MFAU, and MFAO in each myocardial region analyzed and averaged to obtain one value for MBF, MVO<sub>2</sub>, MFAU, and MFAO per subject.

**MEASUREMENT OF MBF.** By applying the image-analysis routine to the time-segmented data, myocardial time-activity curves for each segment were generated. From these data, MBF was quantified in ml/g/min using a previously validated compartmental modeling method (16,17).

**MEASUREMENT OF MVO<sub>2</sub>, MGU, MFAU, AND MFAO.** To measure <sup>11</sup>CO<sub>2</sub> and <sup>11</sup>C-lactate plasma levels, total <sup>11</sup>C-acidic metabolites (<sup>11</sup>C-lactate and <sup>11</sup>CO<sub>2</sub>) were first separated from neutral sugars by trapping them in an ion exchange column (AG1-X4 resin 100 to 200 mesh, formate form). The plasma sample was then eluted through this column with 5 ml of water. Both resin and eluate were counted for radioactivity to obtain the total acidic metabolites and nonmetabolized glucose present. A similar serum sample was also deposited in a test tube, acidified with 6N HCl, sparged with N<sub>2</sub> for 10 min to eliminate the <sup>11</sup>CO<sub>2</sub>, and counted for radioactivity against a sample kept under basic conditions. The count difference between the test tubes was used to calculate the %<sup>11</sup>CO<sub>2</sub> present in the plasma sample. To obtain the %<sup>11</sup>C-lactate, the %<sup>11</sup>CO<sub>2</sub> was subtracted from the total percent of acidic metabolites present in the resin. After correcting PET-derived blood activity for the <sup>11</sup>CO<sub>2</sub> contribution, blood and myocardial time-activity curves were used in conjunction with a one-compartment kinetic model to estimate the rate at which <sup>11</sup>C-acetate is converted to <sup>11</sup>CO<sub>2</sub> ( $k_2$ , min<sup>-1</sup>) (18,19). Values for MVO<sub>2</sub> in  $\mu\text{mol/g/min}$  were then determined using a previously published relationship between  $k_2$  and MVO<sub>2</sub> (19). After correcting PET-derived blood activity for <sup>11</sup>CO<sub>2</sub> and <sup>11</sup>C-lactate, blood and myocardial <sup>11</sup>C-glucose time-activity curves were analyzed with a four-compartment kinetic model to measure fractional myocardial glucose extraction (15). In a similar fashion, after correcting PET-derived blood activity for <sup>11</sup>CO<sub>2</sub>, blood and myocardial <sup>11</sup>C-palmitate time-activity curves were analyzed with a four-compartment kinetic model to measure fractional myocardial palmitate extraction and oxidation (20). These extraction fractions were then used in conjunction with MBF and plasma levels of glucose or free fatty acid to calculate MGU, MFAU, and MFAO (nmol/g/min).

**Measurements of plasma insulin and substrates.** Plasma insulin levels were measured by radioimmunoassay (21). Plasma glucose and lactate levels were measured using a commercially available glucose-lactate analyzer (YSI, Yellow Springs, Ohio). The level of fatty acids in plasma was determined by capillary Gas Chromatography and HPLC (15,20).

**Statistical analysis.** Individual parameter values were averaged and expressed as the mean values  $\pm$  the SD. Comparisons between groups were performed by unpaired  $t$  test;  $p$  values  $< 0.05$  were considered statistically significant.

**Table 1.** Plasma Substrates and Insulin During the PET Study

	Glucose ( $\mu\text{mol/ml}$ )	Free Fatty Acids ( $\mu\text{mol/ml}$ )	Lactate ( $\mu\text{mol/ml}$ )	Insulin ( $\mu\text{U/ml}$ )
Younger (n = 17)	4.8 $\pm$ 0.3	0.67 $\pm$ 0.22	0.68 $\pm$ 0.18	5.9 $\pm$ 2.5
Older (n = 19)	5.1 $\pm$ 0.5	0.60 $\pm$ 0.15	0.92 $\pm$ 0.30*	4.5 $\pm$ 1.7

Values represent mean  $\pm$  SD for measurements obtained throughout the PET study.  
\*p < 0.001.

PET = positron emission tomography.

## RESULTS

**Plasma substrates and insulin.** Shown in Table 1 are the plasma glucose, fatty acid, lactate, and insulin levels averaged for the entire imaging study for the two groups. Plasma glucose and fatty acid levels did not differ between older and younger subjects. However, plasma lactate levels were significantly higher in the older individuals compared with younger subjects ( $p < 0.03$ ). Plasma insulin levels did not differ between the two groups. There were no significant differences in the level of plasma substrates or insulin during the various imaging portions of the study in the younger or the older subjects. Moreover, the percent of variability in these levels did not differ between the two groups.

**Hemodynamics.** Heart rate did not differ between the groups (Table 2). However, both systolic blood pressure ( $p < 0.001$ ) and diastolic blood pressure ( $p < 0.05$ ) were higher in the older subjects compared with younger individuals. As a consequence, the rate-pressure product tended to be higher in the older group (Table 2,  $p < 0.1$ ). There were no differences in the hemodynamic levels during the  $^{15}\text{O}$ -water,  $^{11}\text{C}$ -acetate,  $^{11}\text{C}$ -glucose, and  $^{11}\text{C}$ -palmitate PET studies for either group.

**MBF and MVO<sub>2</sub>.** Shown in Figure 1 are the average values and SDs for the levels of MBF and MVO<sub>2</sub> for the two groups. Values for MBF were similar for younger and older subjects averaging 1.0  $\pm$  0.2 ml/g/min and 1.1  $\pm$  0.3 ml/g/min, respectively,  $p = \text{NS}$ . In contrast, MVO<sub>2</sub> was significantly higher in the older group averaging 5.6  $\pm$  1.6  $\mu\text{mol/g/min}$  compared with the younger group where MVO<sub>2</sub> averaged 4.6  $\pm$  1.0  $\mu\text{mol/g/min}$ ,  $p < 0.05$ , paral-

**Table 2.** Hemodynamics During the PET Study

	HR (beats/min)	SBP (mm Hg)	DBP (mm Hg)	RPP (beats/min $\times$ mm Hg)
Younger (n = 17)	64 $\pm$ 9	111 $\pm$ 12	64 $\pm$ 7	5,087 $\pm$ 1,050
Older (n = 19)	63 $\pm$ 8	130 $\pm$ 19*	71 $\pm$ 10†	5,792 $\pm$ 1,317

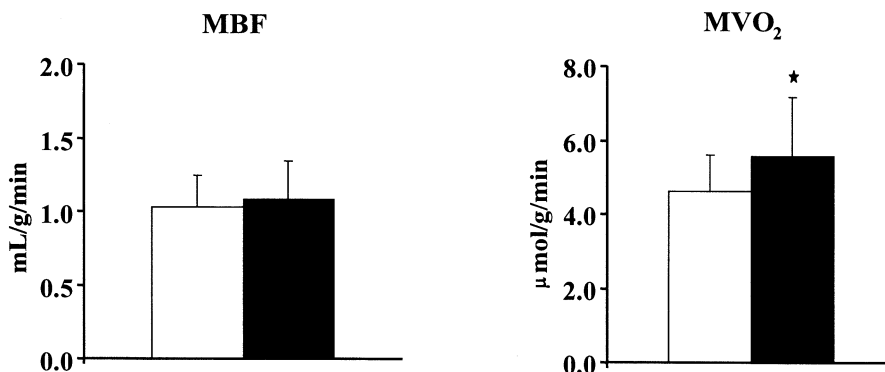
Values represent mean  $\pm$  SD for measurements obtained throughout the PET study.  
\*p < 0.001; †p < 0.05.

DBP = diastolic blood pressure; HR = heart rate; PET = positron emission tomography; RPP = rate pressure product [(SBP + 2·DBP)/3]·HR; SBP = systolic blood pressure.

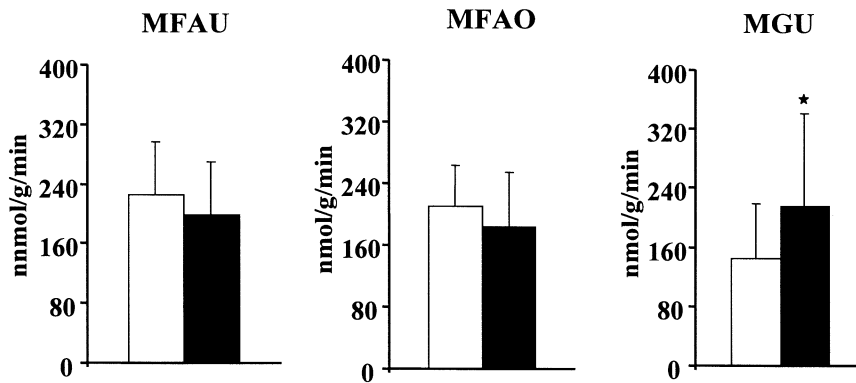
leling the higher systolic and diastolic blood pressures in the older subjects.

**MFAU, MFAO, and MGU.** Shown in Figure 2 are the average values for MFAU, MFAO, and MGU without correction for MVO<sub>2</sub> for the two groups. Values for MFAU did not differ between older subjects (224  $\pm$  71 nmol/g/min) and younger subjects (198  $\pm$  72 nmol/g/min,  $p = \text{NS}$ ). Moreover, differences did not exist in the oxidation of extracted fatty acid as evidenced by comparable MFAO values between older subjects (183  $\pm$  72 nmol/g/min) and younger subjects (209  $\pm$  55 nmol/g/min,  $p = \text{NS}$ ). In contrast, values for MGU were significantly higher in older subjects averaging 215  $\pm$  125 nmol/g/min when compared with younger subjects where values averaged 144  $\pm$  76 nmol/g/min,  $p < 0.05$ .

Increases in myocardial workload can cause a preferential increase in MGU relative to MFAU and MFAO (22). Because the systolic and diastolic blood pressures were higher in the older subjects compared with younger subjects, values for substrate utilization were also corrected for MVO<sub>2</sub> in order to normalize for differences in workload between the two groups (Fig. 3). When this correction was made, the level of MFAU was significantly lower in older subjects (35  $\pm$  10 nmol free fatty acids (FFA)/nmol O<sub>2</sub>  $\times$  10<sup>-3</sup> compared with younger subjects (51  $\pm$  19 nmol FFA/nmol O<sub>2</sub>  $\times$  10<sup>-3</sup>,  $p < 0.005$ ). This decrease in myocardial fatty acid utilization was paralleled by a decrease in fatty acid oxidation as evidenced by MFAO/MVO<sub>2</sub> values of 33  $\pm$  10 nmol FFA/nmol O<sub>2</sub>  $\times$  10<sup>-3</sup> in the older group compared with values of 48  $\pm$  18 nmol FFA/nmol



**Figure 1.** Average values and standard deviations for the levels of myocardial blood flow (MBF) and oxygen consumption (MVO<sub>2</sub>) for the younger and older subjects. Although MBF was similar between the groups, MVO<sub>2</sub> was higher in the older subjects compared with the younger subjects. \*p < 0.05. Open bar = younger subjects; solid bar = older subjects.



**Figure 2.** Average values and standard deviations for the levels of myocardial fatty acid utilization (MFAU) and oxidation (MFAO) and myocardial glucose utilization (MGU). The MFAU and MFAO did not differ between the groups, whereas MGU was higher in the older group compared with the younger group. \* $p < 0.05$ . **Open bar** = younger group; **solid bar** = older group.

$O_2 \times 10^{-3}$  in the younger group ( $p < 0.004$ ). However, correction for  $MVO_2$  resulted in the disappearance in the difference in levels of MGU between older and younger subjects ( $43 \pm 30$  nmol glucose/nmol  $O_2 \times 10^{-3}$  and  $35 \pm 24$  nmol glucose/nmol  $O_2 \times 10^{-3}$ , respectively,  $p = NS$ ). **MFAU, MFAO, and MGU—impact of plasma lactate levels.** Increases in plasma lactate levels have been reported to decrease MFAU and MFAO in experimental animals (11,12). To determine if the higher plasma lactate levels contributed to the switch in substrate metabolism in the older subjects, we correlated values for MFAU/ $MVO_2$ , MFAO/ $MVO_2$ , and MGU/ $MVO_2$  with plasma lactate levels in the younger and older subjects (Fig. 4). No relationship was noted between the plasma lactate levels and the measurements of myocardial fatty acid and glucose metabolism.

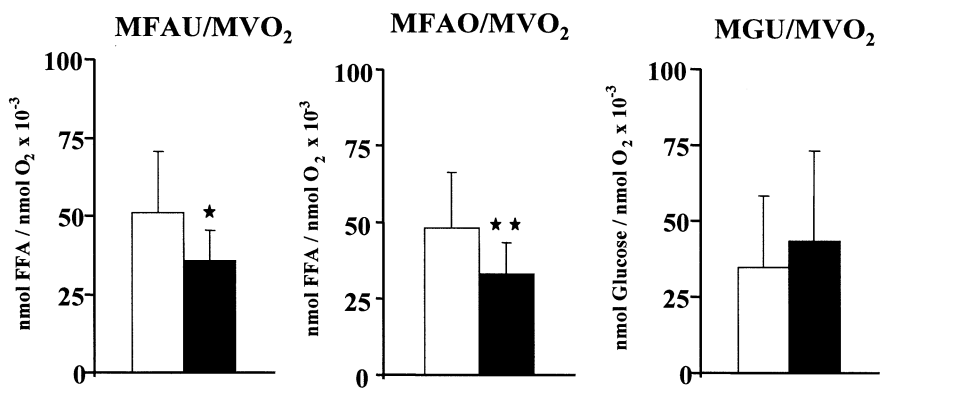
## DISCUSSION

The results of this study are the first to demonstrate that in healthy humans with normal resting systolic function there is an age-related shift in myocardial substrate metabolism. This shift is manifested as an absolute decline in MFAU and MFAO without a change in MGU. As a consequence,

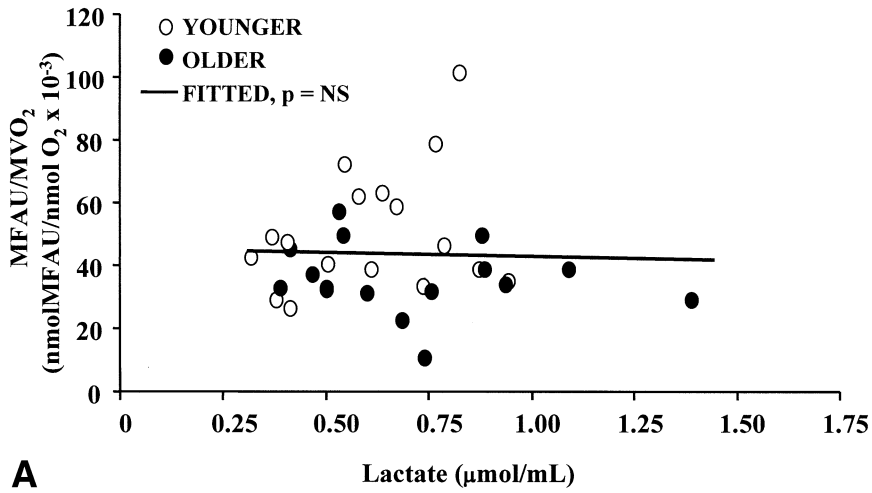
the relative contribution of the MFAU and MFAO to overall substrate metabolism is decreased, and the relative contribution of MGU is likely increased.

**Myocardial metabolism and age.** In the normal adult myocardium, mitochondrial  $\beta$ -oxidation of fatty acids is the primary source of energy production in the fasted state (11,12). In both mouse and rat experimental models of aging, the contribution of MFAO to overall myocardial substrate metabolism declines with age (13,14). It appears the decrease in MFAO is secondary to an age-related decline in carnitine palmitoyltransferase-1 activity, the rate-limiting enzyme for mitochondrial long-chain fatty acid uptake (23). Our results confirm that this age-related decline in MFAO also occurs in the normal human heart. Because both MFAU and MFAO decreased with age, we are unable to determine whether the decline in MFAO was the primary site of the age-related effect on myocardial fatty acid metabolism or if it was secondary to other abnormalities in fatty acid handling by the myocardium such as decreased fatty acid transport across the sarcolemma.

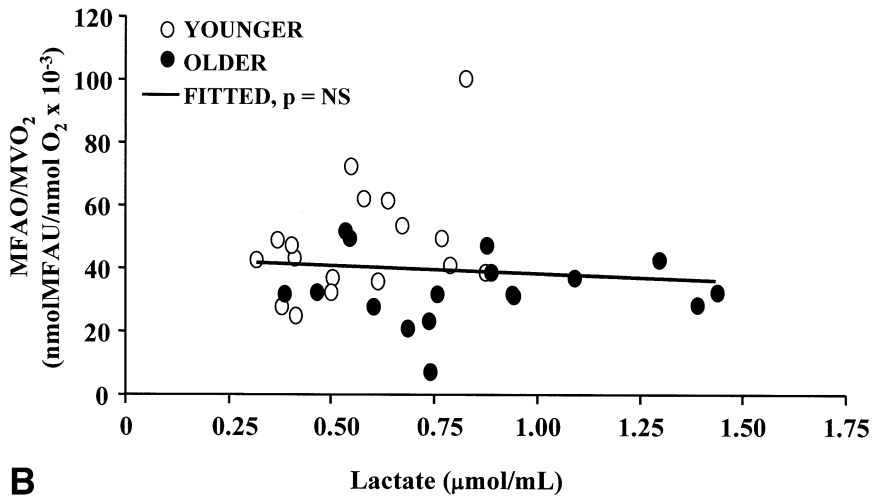
The effects of aging on myocardial glucose metabolism are less clear. In various mouse models of aging, there is an increase in the myocardial protein content for the glucose



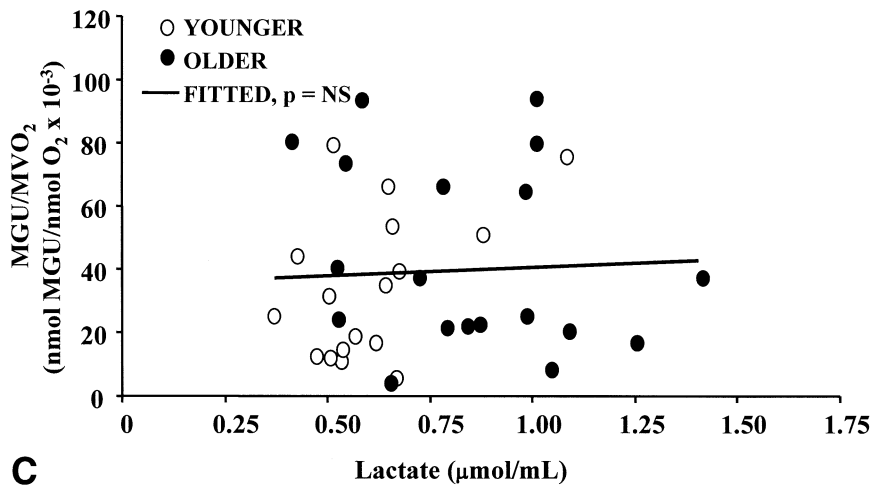
**Figure 3.** Values for myocardial fatty acid utilization (MFAU) and oxidation (MFAO) and myocardial glucose utilization (MGU) all corrected for myocardial oxygen consumption ( $MVO_2$ ). Both MFAU/ $MVO_2$  and MFAO/ $MVO_2$  were lower in the older subjects compared with younger subjects. The MGU/ $MVO_2$  did not differ between the groups. FFA = free fatty acids. \* $p < 0.005$ ; \*\* $p < 0.004$ . **Open bar** = younger subjects; **solid bar** = older subjects.



**A**



**B**



**C**

**Figure 4.** Correlation between plasma lactate levels and values for myocardial fatty acid utilization (MFAU) and oxidation (MFAO) and myocardial glucose utilization (MGU) all corrected for myocardial oxygen consumption (MVO<sub>2</sub>) in both younger and older subjects. There was no relationship between the plasma lactate level and MFAU/MVO<sub>2</sub> (A), MFAO/MVO<sub>2</sub> (B), MGU/MVO<sub>2</sub> (C).

transporter isoform 4 (GLUT-4) suggesting an increase in myocardial glucose uptake (24-26). However, in the rat, myocardial GLUT-4 content decreases with age (27). Yet, glucose metabolism relative to fatty acid metabolism is proportionately increased in hearts of aged rats compared with younger rats (14). Our data are consistent with these latter observations, as we did not observe an absolute increase in MGU (corrected for  $MVO_2$ ) with age. However, we observed that because MFAU declined with age and MGU did not change, the proportional contribution of glucose use to overall substrate utilization relative to fatty acids was increased (Fig. 3).

**Other potential causes for the metabolic shift.** There are many other determinants of the pattern of myocardial substrate use. For example, myocardial fatty acid metabolism is stimulated by increases in plasma fatty acid levels and inhibited by increases in plasma insulin levels (11,12). However, the age-related differences in myocardial fatty acid metabolism we observed cannot be attributed to differences in plasma fatty acid and insulin levels, as they were comparable between the older and normal subjects (Table 1). Plasma lactate levels were slightly, but significantly, higher in the older subjects, the cause of which is unclear. However, this increase in plasma lactate levels did not contribute to the decrease in MFAU and MFAO in the older subjects (Fig. 4). This is consistent with the observation that marked increases in plasma lactate levels (typically 6 to  $8\times$  greater than the levels in the current study) are necessary to suppress MFAU (28,29). That being said, we cannot exclude that myocardial extraction of lactate increased with age, which, in turn, would lead to an increase in myocardial lactate utilization. It is also unlikely that the age differences in fatty acid metabolism we observed were attributable solely to the decline in beta-adrenergic sensitivity that occurs with age (9,10). This is because, in general, catecholamines lead to an increase in glucose uptake, oxidation, and glycogenolysis relative to fatty acid uptake and oxidation (30). Thus, in the state of reduced beta-adrenergic sensitivity, a relative decline in fatty acid metabolism should not have occurred. Increases in cardiac work can preferentially increase MGU relative to MFAU and MFAO (22). The systolic and diastolic blood pressures were higher in the older subjects compared with the younger subjects, which, as expected, was paralleled by a similar increase in  $MVO_2$  in the older subjects. Consequently, we corrected the metabolic measurements for the level of  $MVO_2$ .

The decline in MFAO and, thus, MFAU with age may reflect alterations in mitochondrial lipid content, lipid composition, and protein interactions as well as oxygen free radical injury with subsequent lipid peroxidation of mitochondrial membranes leading to significant membrane dysfunction (31-33). Lastly, the decline in MFAU and MFAO may reflect the metabolic effects of impaired myocardial vasodilator capacity that occur with age (3,4).

**Potential limitations.** We did not show conclusively that glucose supercedes fatty acids as the primary source for the energy production by the myocardium in older humans even though our results demonstrate that, with age, MFAU and MFAO decrease, and MGU remains unchanged. This is because current PET approaches only permit measurements of overall myocardial glucose utilization and, thus, do not provide any information regarding the metabolic fate of extracted glucose. For example, if most of the extracted glucose enters glycogen synthesis as opposed to glycolysis, then little energy production would arise from extracted glucose. However, the finding in experimental models of aging that glycogen content decreases with age makes this scenario less likely (34). Moreover, the current study design could not delineate whether other exogenous substrates such as lactate were being used in lieu of fatty acids in the older subjects. In such a case, the relative proportion of glucose metabolism to overall substrate metabolism might not increase with age. Also, our current methods only permit us to assess the uptake or metabolic fate of tracers of extractable substrates. The currently available methods do not provide any insight into energy produced from endogenous myocardial sources such as triglycerides and glycogen. Thus, the contribution of triglyceride or glycogen breakdown as an energy source is unknown.

**Clinical implications of the metabolic shift.** It remains to be determined what are the clinical implications of this age-related shift in myocardial substrate metabolism. For example, the shift in myocardial substrate towards a lesser dependence on fatty acid metabolism may render the myocardium more resistant to ischemia, demonstrating a beneficial effect. This may be of particular importance because the incidence of coronary artery disease increases with age. In contrast, this age-related metabolic shift may have deleterious consequences. The age-related shift in metabolism may accentuate the switch in substrate metabolism that occurs in both animal models and in humans with pressure-overload-induced left ventricular hypertrophy and in dilated cardiomyopathy.

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