*Brief Report*

# Myocardial Uptake of Circulating Triglycerides in Nondiabetic Patients With Heart Disease

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**Animal studies indicate that oversupply of fatty acids derived from the action of cardiac lipoprotein lipase (LPL) on plasma lipoproteins may contribute to myocardial dysfunction. However, the contribution of circulating triglycerides to myocardial fatty acid supply in humans is not known. Six postabsorptive nondiabetic subjects who were scheduled for diagnostic coronary angiography were studied. $^{14}$C oleate and a lipid emulsion labeled with $^{3}$H triolein were infused to assess myocardial uptake of free fatty acids (FFAs) and triglycerides, as well as myocardial spillover of LPL-generated fatty acids. Six paired blood samples were taken from the femoral artery and the coronary sinus. Coronary sinus concentrations of unlabeled triglycerides were slightly, but not significantly, lower than arterial ($P$ = 0.12), whereas labeled triglyceride concentrations were significantly lower in the coronary sinus than in the artery ($P$ < 0.05; extraction fraction ≅11%). Triglycerides and FFAs accounted for ~17% and ~83%, respectively, of myocardial fatty acid uptake. Systemic and myocardial fractional spillover of LPL-generated fatty acids was 49.0 ± 7% and 34.7 ± 13%, respectively. The myocardium was a minor contributor to systemic triglyceride uptake (~3%) and a trivial contributor to systemic FFA production (~0.5%). These results indicate that circulating triglycerides may be a significant source of fatty acids for myocardial respiration. *Diabetes* 56:527–530, 2007**

It has been suggested that free fatty acids (FFAs) are the primary energy source for the myocardium (1). However, the heart contains a considerable amount of lipoprotein lipase (LPL) (2), and studies in animals have found significant triglyceride uptake by the myocardium. It has been suggested recently that circulating triglycerides are actually the primary lipid fuel for this tissue (3). Very little information on the role of triglycerides in human myocardial metabolism is available, however. The present study was therefore undertaken to determine whether significant uptake of triglycerides occurs in the heart and also to determine the relative role of triglycerides and FFAs in the provision of lipid fuel to that tissue.

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FFA, free fatty acid; LPL, lipoprotein lipase; $LPL_c$, myocardial LPL.

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## RESEARCH DESIGN AND METHODS

Informed written consent was obtained from six Caucasian subjects (three male, three female; average age 65 years, weight 91.3 kg, BMI 30.9 kg/m$^2$) scheduled for diagnostic coronary angiography. Individuals with diabetes, significant hypertriglyceridemia (>2.26 mmol/l), congestive heart failure, unstable angina, recent stroke, previous myocardial infarction or angioplasty, left ventricular ejection fraction <45%, or significant endocrine, hepatic, or renal disorders were excluded. Five of the six subjects proved to have coronary artery disease; four of these underwent percutaneous stent placement. One subject had valve replacement surgery for aortic stenosis.

Subjects were studied according to a protocol approved by the Mayo Institutional Review Board. On the morning of the study (after an overnight fast and after obtaining informed consent), a catheter was placed in a forearm vein for isotope infusion. Infusions of tracer amounts of [9,10-$^{3}$H]triolein (~1.2 μCi/min) and [1-$^{14}$C]oleate (~0.3 μCi/min) were started 90 and 60 min, respectively, before blood sampling; the isotope infusions were continued until blood sampling had been completed as previously described (4). After transfer to the catheterization laboratory, a sheath was placed in the right femoral artery, and a catheter was advanced to the coronary sinus via either the right femoral vein or the right internal jugular vein. After the catheters were positioned, six paired arterial and coronary sinus blood samples were taken at 4-min intervals for measurement of plasma triglyceride concentration and radioactivity, FFA concentration and specific activity, and glucose concentration. Blood gas analysis was also performed to assess the position of the coronary sinus catheter. Heparin was not administered to the subjects until blood sampling was complete.

**Analyses.** Blood samples were collected in chilled 10-ml EDTA tubes containing paraoxon (5) and kept on ice until centrifugation at 4°C. Plasma triglyceride concentrations were determined on a Cobas Mira Plus centrifugal analyzer (4).

Plasma FFA concentration and specific activity (6) and plasma triglyceride radioactivity (4) were determined as previously described. Plasma glucose concentrations were measured using a Beckman Glucose Analyzer II. Arterial blood gasses were determined using a Radiometer America OSM3 Hemoximeter, and hematocrit was determined on an Abbott I-STAT 1 Analyzer.

**Calculations.** All calculations were made using steady-state assumptions. Systemic FFA turnover was calculated using the equations of Steele (7). Global coronary blood flow was estimated to be 120 ml/min in all subjects, based on magnetic resonance estimates of blood flow (8), and an estimated left ventricular plus interventricular septal mass of 158 g (9). Plasma flow was estimated from estimated blood flow and hematocrit. The contribution of the heart to whole-body triglyceride disappearance was calculated by dividing myocardial uptake of labeled triglyceride by the infusion rate of $^{3}$H triolein. Systemic and myocardial FFA and triglyceride kinetics, as well as LPL-generated fatty acid spillover (i.e., escape of fatty acids into the venous effluent from the tissue), were calculated as previously described in a study of forearm metabolism (4).

Mean arterial and coronary sinus values were calculated by averaging results from the six samples taken from each site. Comparisons between arterial and coronary sinus values in the group of subjects were analyzed by a paired $t$ test. Paired $t$ tests (arterial vs. coronary sinus) were performed on triglyceride data in each subject to determine whether significant myocardial uptake was detected.

## RESULTS

Coronary sinus oxygen saturation was <42% in five of the six subjects; it was 67% in one subject, indicating some dilution of the coronary sinus sample with mixed venous blood. Because hematocrit was significantly higher in the

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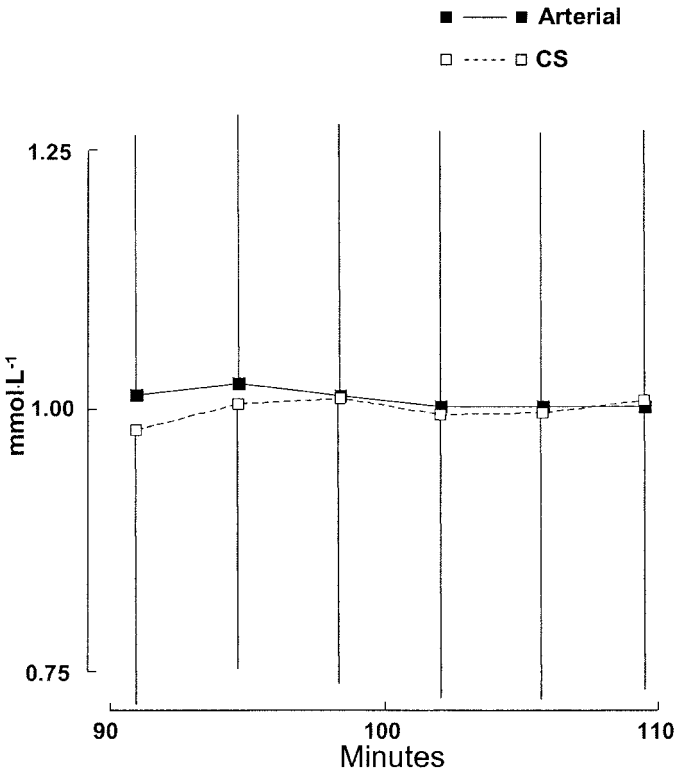


**FIG. 1. Arterial and coronary sinus plasma triglyceride concentrations.**

coronary sinus compared with arterial blood (36.5 ± 1.3 vs. 35.9 ± 1.4%, respectively; $P = 0.024$), coronary sinus concentrations were corrected for hemoconcentration in each subject.

Arterial and coronary sinus triglyceride concentrations and radioactivity are shown in Figs. 1 and 2, respectively. In the six subjects, triglyceride concentrations were slightly, but not significantly, lower in the coronary sinus than in arterial plasma (0.946 ± 0.26 vs. 0.959 ± 0.25 mmol/l, respectively; $P = 0.12$). In a within-subject analysis, coronary sinus concentrations of unlabeled triglyceride were significantly lower than arterial ($P < 0.05$) in three of six subjects. Coronary sinus $^{3}$H triglyceride concentrations were significantly lower than arterial concentrations (2,640 ± 442 vs. 3,009 ± 553 dpm/ml; $P < 0.05$). Myocardial arteriovenous differences of labeled triglyceride were statistically greater than zero in five of six subjects. Myocardial fractional extraction was greater for labeled triglyceride compared with unlabeled triglyceride (10.8 ± 3.3 vs. 2.8 ± 1.6%; $P = 0.035$, data not shown).

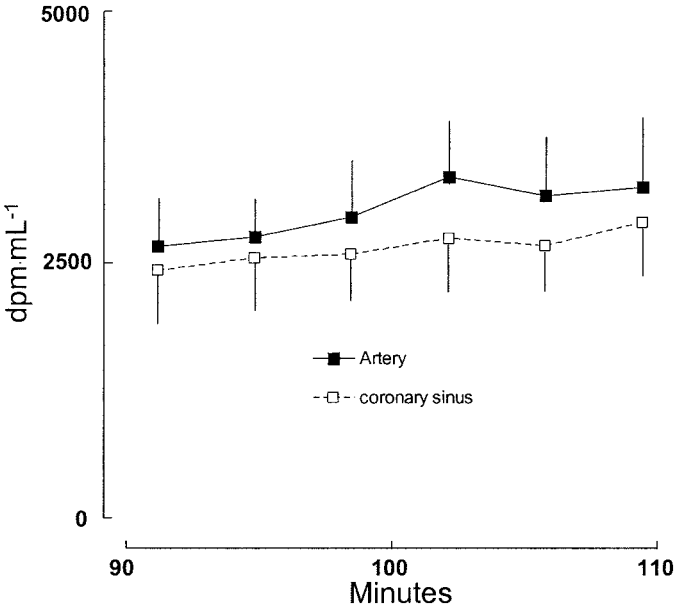


**FIG. 2. Concentrations of $^{3}$H triglyceride in arterial and coronary sinus plasma.**

Table 1 shows plasma oleate and total FFA concentrations, together with plasma $^{14}$C and $^{3}$H specific activities. Coronary sinus concentrations of both oleate and total FFA were significantly lower than arterial ($P < 0.001$). Coronary sinus $^{14}$C oleate specific activities were also lower than arterial ($P = 0.033$). In contrast, $^{3}$H oleate specific activity was not different in coronary sinus and arterial plasma ($P = 0.17$). There was a strong negative correlation between $^{14}$C oleate fractional extraction (34 ± 5%) and plasma oleate concentration ($R = 0.973$, $P < 0.01$, data not shown).

Systemic and myocardial triglyceride and FFA kinetics are shown in Table 2. Uptake of triglycerides averaged 17% of total myocardial fatty acid uptake. Systemic and myocardial fractional spillover of LPL-generated fatty acids was 49 and 34.7%, respectively. Coronary sinus glucose concentration (data not shown) was lower than arterial (4.80 ± 0.31 vs. 5.15 ± 0.21 mmol/l; $P = 0.025$).

## DISCUSSION

The present study demonstrates that the myocardium metabolizes circulating triglycerides in humans and establishes for the first time that the majority of the fatty acids generated by this process are transported into the heart. Previous reports (10,11) suggested triglyceride hydrolysis by the heart, presumably by myocardial LPL ($LPL_c$), but did not determine whether the fatty acids generated were taken up by the myocardium or whether they spilled over into the systemic circulation. The extraction of unlabeled triglyceride in the present study was significant in 3 of 6 subjects, but not for the group ($P = 0.12$), consistent with a previous report in which significant uptake of unlabeled triglyceride was observed in 9 of 17 subjects (11); this is likely a reflection of the difficulty in detecting very small arteriovenous concentration differences. The extraction of labeled triglyceride in our study, on the other hand, was significant in five of six subjects and for the group as a whole ($P < 0.05$). These observations indicate a significant potential role for circulating triglycerides as a source of fuel for myocardial metabolism. It has been suggested that measurements in subjects with heart disease may generally reflect normal myocardial metabolism in the absence of heart failure or active ischemia, since myocardial FFA uptake, glucose uptake, and lactate balance in individuals with coronary artery disease is not different than that observed in young healthy volunteers (12). Nonetheless, caution should be exercised in extrapolating our findings in a small group of individuals with heart disease to other populations.

Studies in mice indicate that circulating triglycerides actually contribute the majority of fatty acids for myocardial respiration (3). Our results are consistent with previous work, suggesting that FFAs are the majority contributor in humans, at least under postabsorptive conditions (11–13). Triglyceride fractional extraction was 2.8%

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TABLE 1
Plasma oleate and total FFA concentrations and plasma oleate specific activities

| Time (min) | 90 | 94 | 98 | 102 | 106 | 110 |
|---|---|---|---|---|---|---|
| Oleate concentration (μmol/l) | | | | | | |
| Arterial | 233 ± 33 | 227 ± 41 | 217 ± 29 | 220 ± 27 | 222 ± 36 | 239 ± 28 |
| Coronary sinus* | 181 ± 45 | 189 ± 33 | 189 ± 49 | 168 ± 33 | 169 ± 39 | 166 ± 36 |
| Total FFA concentration (μmol/l) | | | | | | |
| Arterial | 711 ± 107 | 689 ± 127 | 632 ± 101 | 650 ± 93 | 615 ± 55 | 648 ± 51 |
| Coronary sinus* | 494 ± 67 | 552 ± 82 | 531 ± 58 | 498 ± 66 | 517 ± 69 | 485 ± 71 |
| $^{14}$C oleate specific activity (dpm/nmol) | | | | | | |
| Arterial | 1.12 ± 0.19 | 1.29 ± 0.018 | 1.30 ± 0.20 | 1.42 ± 0.21 | 1.47 ± 0.16 | 1.29 ± 0.19 |
| Coronary sinus† | 1.09 ± 0.16 | 1.11 ± 0.19 | 1.30 ± 0.25 | 1.26 ± 0.18 | 1.34 ± 0.14 | 1.20 ± 0.14 |
| $^{3}$H oleate specific activity (dpm/nmol) | | | | | | |
| Arterial | 3.92 ± 0.96 | 4.38 ± 0.90 | 4.61 ± 0.96 | 4.69 ± 0.95 | 4.72 ± 0.96 | 4.56 ± 1.20 |
| Coronary sinus | 4.64 ± 0.94 | 4.46 ± 1.00 | 4.71 ± 0.95 | 4.82 ± 1.02 | 5.00 ± 1.12 | 4.47 ± 0.97 |

Data are means ± SE. *$P < 0.001$ vs. arterial; †$P = 0.033$ vs. arterial.

in our study, similar to the findings of Lassers et al. (11). It should be acknowledged that secretion of triglyceride-containing lipoproteins by the heart, which has been reported in rodents (14), would result in an underestimate of myocardial uptake of circulating triglycerides.

Measurement of arterial-coronary sinus concentration differences of labeled or unlabeled triglyceride could overestimate myocardial uptake of triglyceride fatty acids if there were spillover of $LPL_c$-generated fatty acids. The spillover phenomenon has previously been demonstrated in the forearm (4,15) and in adipose tissue (15). Myocardial uptake of an exogenously labeled triglyceride tracer has not previously been investigated in humans. The present study estimates fractional spillover of $LPL_c$-generated fatty acids from a chylomicron-like particle to be ~35%. We found fractional extraction of the labeled emulsion to be ~11% or approximately fourfold higher than the extraction of unlabeled triglyceride. This indicates a preference by $LPL_c$ for larger chylomicron-sized particles, as has been previously observed in forearm (4) and adipose tissues (16). In contradistinction to chylomicrons, systemic spillover from VLDL triglyceride appears to be negligible (17).

It is possible that dietary fat is a major direct source of myocardial fatty acid uptake. No data on myocardial uptake of meal fat is available in humans, but the amount of triglyceride fatty acids traversing the circulation in subjects consuming high-fat diets is similar to the amount of FFA released in a 24-h period, ~100 g/day in a 70-kg individual (4).

TABLE 2
Kinetic data

| | |
|---|---|
| Systemic | |
| Oleate turnover (μmol/min) | 270 ± 65 |
| FFA turnover (μmol/min) | 749 ± 165 |
| Fractional spillover (%) | 49.0 ± 6.9 |
| Myocardial | |
| FFA uptake (μmol/min) | 15.2 ± 1.4 |
| FFA uptake (% of systemic) | 3.1 ± 1.1 |
| FFA release (μmol/min) | 3.8 ± 0.9 |
| FFA release (% of systemic) | 0.5 ± 0.1 |
| FFA fractional extraction (%) | 34 ± 5 |
| TG fatty acid uptake (μmol/min) | 3.1 ± 2.5 |
| $^{3}$H TG uptake (% of systemic) | 1.9 ± 0.5 |
| Total fatty acid uptake (μmol/min) | 18.3 ± 2.8 |
| Contribution of TGs to total fatty acid uptake(%) | 17.1 ± 8.5 |
| Fractional spillover (%) | 34.7 ± 13.0 |

Data are means ± SE. TG, triglyceride.

The release of unlabeled FFA into the coronary sinus in the present study presumably derives from the action of hormone-sensitive lipase in epicardial fat. This is trivial in systemic terms, however, accounting for only ~0.5% of whole-body FFA appearance. It is unlikely that the triglyceride uptake observed in the present study occurred in epicardial fat, in view of the low spillover of $LPL_c$-generated fatty acids observed. We found an average fractional spillover of ~35%, much lower than previously reported for adipose tissue, which is ~80% several hours after meal ingestion (15).

The present study provides the first available estimates of the contribution of the heart to whole-body FFA and triglyceride metabolism. When heterozygous LPL knockout mice were crossbred with mice possessing human $LPL_c$ to create a mouse with $LPL_c$ activity only, the animals had near-normal circulating triglyceride levels and normal HDL levels in spite of the absence of LPL in adipose tissue and skeletal muscle (18). This suggests that $LPL_c$ may be an important contributor to whole-body LPL activity. Our data indicate that only ~2% of whole-body triglyceride disappearance and ~3% of systemic FFA uptake occurs in the heart in postabsorptive humans. This is the case in spite of the fact that most myocardial ATP production is derived from FFA oxidation after an overnight fast (19). Although no data are available on myocardial metabolism during meal absorption, the heart readily switches to carbohydrate oxidation during infusion of insulin and glucose (20).

It is not known with certainty whether myocardial uptake of triglyceride fatty acids from blood is essential for optimal myocardial energetics, but animals deficient in $LPL_c$ apparently have normal cardiac function (21). The fact that the heart can take up and oxidize large amounts of carbohydrate when deprived of FFA (20), together with the avid extraction of FFA from blood as shown in the present and previous studies, would suggest that circulating triglycerides are not an essential fuel for this tissue.

On the other hand, $LPL_c$ may represent a route for oversupply of fatty acids to the myocardium. Expression of an abnormal $LPL_c$ on the surface of cardiomyocytes in mice leads to increased intracardiomyocellular lipid accumulation and a cardiomyopathy (22). Increased triglyceride accumulation in cardiac muscle has been shown in humans (23,24), although the relative contributions of FFAs and circulating triglycerides to this phenomenon are

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not known. This accumulation of lipid may be a major contributor to contractile dysfunction and even nonischemic cardiomyopathy (25). Additional research will be required to assess myocardial uptake of circulating triglycerides during meal absorption.

In summary, the present study confirms that the myocardium takes up fatty acids from circulating triglycerides in humans. The magnitude of postprandial triglyceride fatty acid uptake is unknown. Studies in postabsorptive hypertriglyceridemic subjects and after ingestion of a mixed meal are needed to improve our understanding of the contribution of circulating lipids to myocardial energy supply.

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