Acute intralipid infusion reduces cardiac luminal lipoprotein lipase but recruits additional enzyme from cardiomyocytes

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Abstract

Objective: Lipoprotein lipase (LPL) metabolizes the triglyceride (TG) core of lipoproteins. We evaluated whether circulating lipids can regulate LPL by influencing the transfer of enzyme from the myocyte to the endothelial lumen.

Methods: Acute intralipid (IL, 10% and 20%) infusion was performed in male Wistar rats. After 3 h, insulin resistance was assessed using a euglycemic hyperinsulinemic clamp. Cardiac LPL activity was determined by retrogradely perfusing the hearts with heparin. Immunogold electron microscopy visualized LPL, and heparanase was detected by immunofluorescence. Cardiac myocytes were also isolated, and heparin-releasable LPL activity was measured.

Results: IL infusion increased both plasma and cardiac lipids. Circulating basal plasma LPL activity increased for the duration of the infusion. Compared to control (CON) hearts, there was a substantial decrease in heparin-releasable LPL activity at the vascular lumen following 3 h of IL infusion, an effect unrelated to changes in gene and protein expression or whole-body insulin resistance. Although constant perfusion of CON hearts with heparin stripped off most of the luminal bound LPL, hearts from IL-infused animals continued to release excessive amounts of the enzyme, suggesting buildup of LPL within endothelial cells or at the endothelial basolateral surface. Immunogold labeling confirmed this observation and demonstrated robust anti-LPL staining at these sites, only in IL hearts. Perfusing hearts from IL-rats in vitro, in the absence of TG, allowed the accumulated enzyme pool to transfer to the coronary lumen.

Conclusion: Our data suggest that acute amplification of lipids reduces cardiac luminal LPL but facilitates additional recruitment of cardiomyocyte enzyme. Should this mechanism occur globally, it could contribute towards management of hyperlipidemia.

Keywords: Intralipid; Heart; LPL; Fatty acid; Heparanase

1. Introduction

Plasma triglycerides (TG) are maintained through uptake from the gut, secretion from the liver, and clearance by vascular endothelium-bound lipoprotein lipase (LPL). LPL actively metabolizes the TG core of lipoproteins [very low density lipoproteins (VLDL) and chylomicrons] to fatty acid (FA), which are then transported into the underlying tissue for numerous metabolic and structural functions [1]. Through such a role, LPL activity directly affects the level of circulating lipoprotein-TG [1]. Thus, in transgenic rabbits that have global overexpression of LPL, attenuation of hypertriglyceridemia is observed [2]. Additionally, administration of NO-1886, an
LPL-activating agent, to high-fat fed animals, suppressed hypertriglyceridemia [3].

Although the functional location of LPL-mediated lipoprotein hydrolysis is at the capillary endothelial cell surface, a number of approaches including in situ hybridization have failed to demonstrate LPL mRNA localization in endothelial cells [4]. In tissues like heart and adipose, this enzyme is produced in cardiomyocytes and adipocytes respectively [5], and subsequently secreted onto heparan sulphate proteoglycan (HSPG) binding sites on the surface of these cells. From here, LPL is transported onto comparable binding sites on the luminal side of endothelial cells [5–8]. Thus, in the heart, electron microscopy using immunogold-labeling established that 78% of total LPL is present in cardiac myocytes, 3–6% in the interstitial space, and 18% at the coronary endothelium [5,8]. Even though the majority of enzyme is located in myocytes, vascular endothelial-bound LPL likely determines the rate of plasma lipoprotein-TG clearance, and hence is termed “functional” LPL [9]. LPL also mediates a non-catalytic bridging function that allows it to bind simultaneously to both lipoproteins and specific cell surface proteins, facilitating cellular uptake of lipoproteins [10].

Functional LPL is regulated by multiple mechanisms. Thus, gene mutations produce inactive LPL monomers leading to abnormal binding to HSPG [11]. LPL at the endothelial lumen is also managed by internalization of the HSPG–LPL complex into an endothelial endocytotic compartment [12]. Finally, FA can directly detach the enzyme from its HSPG binding sites [13]. An additional property of FA, demonstrated in vitro, is its ability to increase heparanase expression in endothelial cells [14]. In adipocytes, heparanase regulates LPL by enhancing its release through cleavage of HSPG, an effect suggested to influence transfer of LPL from parenchymal cells to the endothelial lumen [14,15]. The aim of the present study was to determine whether these effects of FA occur in vivo, using the heart as a model system in which we can differentiate LPL in various compartments. Our data suggests that acute amplification of plasma FA reduces cardiac luminal LPL but recruits additional enzyme from cardiomyocytes.

2. Methods and materials

2.1. Animals

The investigation conforms to the guide for the care and use of laboratory animals published by the US National Institutes of Health and the University of British Columbia (animal care certificate A00-0291). Male Wistar rats (250–300 g) were obtained from the University of British Columbia Animal Care Unit and fed a standard laboratory diet (PMI Feeds, Richmond, VA), and water ad libitum. Animals were anaesthetized with sodium pentobarbital (Somnotol; 65 mg/kg), and the left jugular vein cannulated. Intralipid (IL; 5 ml/kg/h) [16] or vehicle (saline, CON) were then infused over a period of 3 h. Where indicated, IL infusion at the third hour was terminated, and the animals kept for another 3 h before removal of hearts.

At the 3h, blood samples (370 μl) were collected (within 30 s) from 4 control and 4 IL animals through a tail vein incision. After centrifugation, plasma was used for analysis of FA, TG and LPL.

2.2. Measurement of whole-body insulin resistance

Whole-animal insulin resistance was assessed using a euglycemic–hyperinsulinemic clamp, as described previously [17]. This procedure involves the simultaneous intravenous infusion of insulin (to inhibit endogenous hepatic production) and glucose; the quantity of exogenous glucose required to maintain euglycemia is a reflection of the net sensitivity of target tissues (mainly skeletal muscle) to insulin. Briefly, after infusion of vehicle or IL for 3 h, animals were anesthetized with sodium pentobarbital (Somnotol; 65 mg/kg) and a cannula inserted into the left jugular vein. Insulin (Humulin R; 3 mU/min/kg) and D-glucose (50%) were continuously delivered for 2 h, with the glucose infusion started 4 min after commencement of insulin infusion. At regular intervals, a drop of blood taken from the tail vein was analyzed for glucose (using a glucometer: AccuSoft Advantage). The glucose infusion rate was adjusted accordingly to maintain euglycemia.

2.3. Quantification of TG and FA

Total lipids were extracted from plasma and heart, and solubilized in chloroform–methanol–acetone–hexane (4:6:1:1 vol/vol/vol/vol). Separation of TG and FA was achieved with an HPLC (2690 Alliance HPLC, Waters, Milford, MA). FAs were quantified as their respective methyl esters, with heptadecaenoic acid (17:0) used as the internal standard, with a Varian 3400 gas–liquid chromatograph equipped with a flame ionization detector, a Varian Star data system, and an SP-2330 capillary column (30 m × 0.25 mm ID; Supelco, Bellefonte, PA).

2.4. Plasma LPL activity

Plasma LPL activities following vehicle and IL infusion were determined as described previously [18]. Briefly, blood samples were collected at 1 h intervals during IL infusion, and plasma was separated and stored at −70 °C until assayed for LPL activity. Plasma lipase activity was determined by first measuring total lipase (hepatic+LPL) activity in 5 μl of plasma sample. Hepatic lipase activity was measured by incubating plasma with 1 M NaCl (at room temperature for 10 min before exposure to substrate), and conducting the assay in the absence of apolipoprotein CII [19], to suppress LPL activity. Plasma LPL activity was calculated as the difference between total and hepatic lipase activity.

2.5. Isolated heart perfusion and LPL activity

At termination, hearts from the different groups were removed and immersed in cold (4 °C) Krebs HEPES buffer.
containing 10 mM glucose (pH 7.4). After the aorta was cannulated and tied below the innominate artery, hearts were perfused retrogradely by the nonrecirculating Langendorff technique as described previously [17]. Perfusion fluid was continuously gassed with 95% O₂/5% CO₂ in a double-walled, water-heated chamber maintained at 37 °C with a temperature-controlled circulating water bath. The flow rate was controlled at 7–8 ml/min. Perfusion solution was then changed to buffer containing 1% fatty acid-free BSA and heparin (5 units/ml) to determine endothelium-bound LPL. Coronary effluent was collected in timed fractions over 10 min, and assayed for LPL activity by measuring the hydrolysis of a sonicated [³H]triolein substrate emulsion [17].

To observe coronary luminal LPL recovery in vivo, some animals were maintained for another 3 h following termination of 20% IL infusion. Hearts were removed and perfused with heparin to measure endothelial-bound LPL activity, as described previously. In a separate experiment, hearts from IL infused rats were perfused with heparin for 2 min (to deplete the LPL pool at the coronary lumen), allowed to recover for 1 h during which the heart was perfused with heparin-free Krebs buffer, and a second 10 min perfusion with heparin was then performed to determine the extent of LPL recovery in vitro.

2.6. LPL gene expression and protein

Following termination of 20% IL infusion, LPL gene and protein expression were measured using RT-PCR and Western blotting as described previously [17,20]. For Western blotting, 100 mg of homogenized ventricular tissue and the 5D2 monoclonal mouse anti-bovine LPL (generously provided by Dr. J. Brunzell, University of Washington, Seattle, WA) were used.

2.7. Immunogold-labeled electron microscopy

Immunogold electron microscopy was used to visualize LPL following IL infusion. Briefly, CON and 20% IL hearts were perfused for 15 min with 4% paraformaldehyde. Following removal and sectioning, tissues were kept for another 2 h in this fixative before embedding in gelatin blocks. Ultrasections using an ultramicrotome were collected on gold grids (200 mesh) for transmission electron microscopy. The grids were treated with 150 mM ammonium chloride in phosphate buffer saline (PBS)–glycine solution, and then blocked in 1% ovalbumin in PBS–glycine solution at room temperature. The grids were then incubated with primary antibody (5D2), at a dilution of 1:200 overnight at 4 °C in a blocking solution. Sections were then incubated with a secondary antibody (sheep anti-mouse IgG gold-conjugated, 10 nM) for 2 h at room temperature, at a dilution of 1:100. Sections were stained for 4 min with a saturated uranyl acetate solution. Electron micrographs were obtained using a Philip 300 transmission electron microscope. Distribution of immunogold-labeled LPL was quantified by a previously described method [5]. Briefly, 10 fields from each heart section were selected randomly and printed as electron micrographs at ×60,000. The micrographs (20 by 25 cm) were digitalized and examined using image analysis software (Image J, NIH). Following counting of the number of particles in endothelial and subendothelial compartments, and measuring the area of the compartments by conventional morphometry, the density of immunogold particles was calculated by dividing the number of particles by the area.

2.8. Myocyte surface LPL activity

In addition to LPL at the coronary endothelial lumen, considerable amount of LPL is also located on the myocyte surface and within myocytes. To examine LPL activity released from the surface of cardiomyocytes, ventricular calcium-tolerant myocytes were prepared by a previously described procedure [20]. Cardiac myocytes from CON and 20% IL hearts were suspended at a final cell density of 0.4×10⁶ cells per ml, incubated at 37 °C and basal LPL activity in the medium measured. To release surface-bound LPL activity, heparin (5 U/ml) was added to the myocyte suspension and aliquots of cell suspension were removed at

Fig. 1. Acute intralipid infusion induces insulin resistance. Following infusion of vehicle or IL (10% and 20%, 5 ml/kg/h) for 3 h, whole-animal insulin resistance was assessed using a euglycemic–hyperinsulinemic clamp. Insulin (HumulinR; 3 mU/min/kg) and D-glucose (50%) were continuously delivered (by a cannula inserted into the left jugular vein) for 2 h. At regular intervals, blood samples taken from the tail vein were analyzed for glucose using a glucometer. The glucose infusion rate (GIR) was adjusted accordingly to maintain euglycemia. BG, blood glucose. Results are the means ± S.E. of 3–4 animals in each group. CON, control; IL, intralipid. *Significantly different from control, P<0.05.
different time points, medium separated by centrifugation in an Eppendorf microcentrifuge, and assayed for LPL activity.

2.9. Immunolocalization of heparanase

Heparanase immunolocalization was assessed in myocardial sections by a previously described procedure [21]. Briefly, hearts from CON and 20% IL animals were fixed in 10% formalin for 24 h. Blocks were then embedded and sectioned. For immunostaining, sections were deparaffinized, rehydrated, and treated with 5% (vol/vol) heat inactivated goat serum in TBS to block non-specific background. Sections were incubated with rabbit polyclonal primary antibody against heparanase 1 (Santa Cruz, 1:300) overnight at room temperature in a humid chamber. Samples were then washed with PBS and incubated for 1 h at room temperature with the secondary antibody goat anti-rabbit IgG-FITC (Santa Cruz, 1:500 dilution). The unbound fluorescent probe was rinsed with PBS buffer and sections mounted with DABCO. Slides were visualized using a Bio-Rad 600 Confocal Microscope at 630× magnification.

2.10. Materials

[^3H]triolein was purchased from Amersham Canada. Heparin sodium injection (Hapalean; 1000 USP U/ml) was

**Fig. 2.** Intralipid augments both plasma and cardiac lipids. Animals were anaesthetized and the left jugular vein cannulated. Intralipid (IL, 10% and 20%; 5 ml/kg/h) was infused over a period of 3 h. At the third hour, blood samples were collected and centrifuged. Hearts were also removed at this time, and plasma and cardiac samples were used for HPLC analysis of fatty acids (FA) and triglyceride (TG). Data are mean±S.E. for 4 rats in each group. *Significantly different from control (CON), P<0.05.

**Fig. 3.** Plasma and cardiac LPL activity changes following IL. Plasma LPL activity in the basal state was determined in control and IL rats. Following blood sample collection, LPL activity was determined by first measuring total lipase (hepatic+LPL) activity. Incubating plasma with 1 M NaCl, and conducting the assay in the absence of apolipoprotein CII, to suppress LPL activity, measured hepatic lipase activity. Plasma LPL activity was calculated as the difference between total and hepatic lipase activity (A). CON and IL hearts were removed and the isolated hearts were perfused retrogradely with heparin (5 U/ml), and fractions of perfusate collected and analyzed for LPL activity. The rapid heparin induced LPL discharge (0–2 min), suggested to represent LPL located at or near the endothelial luminal cell surface, is depicted in the left panel (B). The right panel (B) likely represents LPL that originates from within endothelial cells, interstitial space or myocyte cell surface. Changes in LPL activity in response to heparin perfusion, over time, were analyzed by multivariate ANOVA followed by the Newman–Keul’s test using the Number Cruncher Statistical System. LPL gene and protein expressions were also measured in isolated hearts from CON and 20% IL animals, using RT-PCR and Western blotting (C), respectively. Results are the mean±SE of four rats in each group. *P<0.05 vs. control. CON, control; IL, intralipid.
obtained from Organon Teknika. All other chemicals were obtained from Sigma Chemical.

2.11. Statistics

Values are means±S.E. LPL activity in response to heparin perfusion over time was analyzed by multivariate (two-way) ANOVA using the Number Cruncher Statistical System. Wherever appropriate, one-way ANOVA followed by the Tukey or Bonferroni test or the unpaired and paired Student’s \( t \) test was used to determine differences between group mean values. The level of statistical significance was set at \( P<0.05 \).

3. Results

3.1. Acute IL infusion affects insulin sensitivity

Acute IL infusion has been reported to induce insulin resistance [16]. In our current study, using the euglycemic–hyperinsulinemic clamp, 10% IL did not alter whole-body
insulin sensitivity. However, 20% IL for 3 h significantly reduced the glucose infusion rate (GIR), suggesting the presence of insulin resistance (Fig. 1).

3.2. Increased plasma and cardiac lipids following IL infusion

After 3 h, IL infusion dose-dependently increased both plasma FA and TG (Fig. 2A). These augmented circulating lipids were closely associated with elevated cardiac FA and TG accumulation (Fig. 2B).

3.3. IL changes plasma and heparin-releasable cardiac LPL activity

Within 1 h of 10 and 20% IL infusion, circulating basal LPL activity increased and remained high for the duration of the infusion (Fig. 3A). LPL at the coronary lumen is an outcome of translocation of the enzyme from the myocyte cell surface [5]. To determine whether IL influences LPL at the vascular lumen, isolated hearts from CON and IL infused rats were perfused retrogradely with heparin buffer, which resulted in rapid LPL discharge, and peak activity, likely representing LPL located at or near the endothelial surface, was observed within 2 min. Compared to CON hearts, there was a substantial decrease in peak coronary heparin-releasable LPL activity at the vascular lumen following 3 h of 10 or 20% IL infusion (Fig. 3B, left panel), an effect unrelated to changes in LPL gene and protein expression (Fig. 3C). Interestingly, although constant perfusion of control hearts with heparin was able to strip off most of the luminal bound LPL, hearts from IL infused animals continued to release excessive amounts of the enzyme (Fig. 3B, right panel), suggesting buildup of enzyme within...
endothelial cells or at the endothelial basolateral surface. As this effect was most pronounced with infusion of 20% IL, all of the subsequent experiments were carried out using this concentration of IL.

### 3.4. Immunogold labeling for LPL

Based on our LPL activity data, suggesting accumulation of enzyme within endothelial cells and/or at the basolateral surface of the endothelial cells in 20% IL hearts, we used the immunogold technique to identify and confirm the subcellular localization of cardiac LPL. In both CON and IL hearts, there was a strong gold-particle labeling for LPL in myocytes. No or few gold particles were observed at the basement membranes adjacent to endothelial cells or within these cells in CON hearts (Fig. 4A and B). Only IL hearts demonstrated robust anti-LPL immunogold labeling at the above sites (Fig. 4A and B). The electron micrograph also illustrates increased lipid-like vacuoles in myocytes following IL treatment.

### 3.5. Decrease in myocyte LPL activity is coupled to augmented endothelial heparanase

In the heart, the majority (78%) of LPL is present in cardiac myocytes [5], which subsequently transfers onto luminal HSPG binding sites. In our current study, we evaluated if 20% IL can decrease this myocyte enzyme pool, suggesting LPL transfer to the luminal surface. There was a significant decrease in heparin-releasable LPL activity from myocytes isolated from IL hearts compared with CON (Fig. 4C). Increased lipids can augment synthesis and release of heparanase from the endothelium. As this heparanase is preferentially

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**Fig. 6.** Reversal of changes in LPL following decreased TG both in vivo and in vitro. Following 3 h of 20% IL, the infusion was terminated and the animals kept for another 3 h before removal of hearts. At each 1 h interval, blood samples were obtained from the tail vein for analysis of plasma TG levels (A). Hearts were then perfused with heparin to measure LPL activity (B) as described in Fig. 3. In a separate experiment, hearts from 3 h 20% IL infused rats were exposed to heparin (2 min) (left panel, C), followed by 1 h wash with Kreb’s buffer. A second heparin perfusion (10 min) was then performed to determine the extent of LPL recovery (right panel, C). Results are the mean±S.E. of four rats in each group. *P<0.05 vs. control. CON, control; IL, 20% intralipid; T-IL, 3 h following termination of 20% IL infusion.
secreted to the basolateral rather than the luminal side [14], it could facilitate LPL translocation from the myocyte to the subendothelium and endothelium. Using immunofluorescent detection, we identified higher heparanase in coronary endothelium following IL (Fig. 5).

3.6. Reversal of changes in LPL following reduction in TG both in vivo and in vitro

In an effort to observe whether changes in cardiac LPL are reversed following reduction in TG, 20% IL infusion was terminated, and animals kept for another 3h. Although plasma TG dropped rapidly on termination of IL infusion, hypertriglyceridemia was still apparent after 3 h (Fig. 6A). Measurement of LPL indicated that although peak heparin releasable LPL activity returned to normal in IL hearts (Fig. 6B, left panel), on continuous perfusion of these hearts with heparin, more LPL was released compared to CON (Fig. 6B, right panel). An alternate approach involved rapid removal of luminal LPL with heparin (Fig. 6C, left panel), followed by in vitro perfusion with TG free buffer for 1 h. Using this strategy, the enzyme built up in IL hearts was able to transfer to endothelium luminal HSPG, such that with a second heparin perfusion, peak LPL activity was observed within 2 min, was substantially higher than CON, and was followed by a rapid decline (Fig. 6C, right panel).

4. Discussion

A number of mechanisms have been proposed to modulate endothelium-bound lipoprotein lipase (LPL) activity. Vascular endothelial cells can internalize LPL [12]. In addition, fatty acid (FA) released through the action of LPL can decrease enzyme activity by product inhibition [22] or by reducing apolipoprotein (apo) CII activation of the enzyme [23]. A third mechanism has been proposed, based on experiments where FA, both in vivo and in vitro, caused displacement of LPL from endothelial heparan sulphate proteoglycan (HSPG) binding sites [13]. In the present study, our data suggest that increased circulating lipids can also facilitate LPL transfer from cardiomyocytes to the endothelium.

Acutely infusing intralipid (IL) augmented both plasma FA and triglyceride (TG) in a dose dependent manner. As previous studies have reported that lipids can displace LPL from endothelial cells [13,24], we measured basal plasma LPL activity and found a progressive increase of enzyme with both 10% and 20% IL. As HSPG-bound LPL exhibits a disparate rate of lipolysis compared with conventional lipolysis assays with LPL in solution, it has been suggested that such displacement greatly facilitates TG hydrolysis and lipoprotein clearance [14]. Several organs like skeletal muscle and adipose tissue could contribute towards this increase in plasma LPL. However, as perfusion of these organs to determine vascular endothelial LPL in vitro is complicated, we measured heparin releasable LPL activity in hearts from IL infused rats. Unlike other organs, the heart is unique in that following isolation, LPL at the coronary endothelium, interstitial space and cardiac myocytes can be determined simultaneously [5]. Heparin perfusion of 10% and 20% IL hearts for 2 min (that releases LPL localized predominantly from coronary lumen) released LPL activity that was lower compared to control (CON). This decrease in coronary luminal LPL activity could not be explained by changes in insulin sensitivity, and was unrelated to alterations in LPL gene expression. As LPL protein measured in total heart homogenates remained unchanged between CON and IL infused rats, it is likely that this specific decrease in luminal LPL activity is posttranslational, and includes displacement of
the enzyme as a result of high circulating plasma lipid. Alternatively, the reduced cardiac luminal LPL could be a consequence of the effect of linoleic acid. A key component of IL, soy oil, contains 40–60% linoleic acid, 20–30% oleic acid, and 5–15% palmitic acid. Linoleic acid is known to inhibit proteoglycan synthesis, in addition to decreasing the anionic properties of HSPG in endothelial cell monolayers [25].

Interestingly, following prolonged heparin perfusion of IL hearts, a second prominent phase of LPL release was observed, that was more pronounced in 20% IL infused rats. It is possible that this delayed heparin releasable LPL could originate from vesicles within endothelial cells, from enzyme that accumulated at the basolateral surface of vascular endothelium, or from the myocyte cell surface [8]. Indeed, 20% IL hearts demonstrated robust anti-LPL immunogold labeling at basement membranes adjacent to endothelial cells or within these cells. Both of these sites may be accessible to heparin, which has been demonstrated to traverse the arterial wall [26].

Heparanase is an enzyme that specifically cleaves heparan sulfate glycosaminoglycans from HSPG core proteins [27]. In studies using adipocytes and endothelial cells, FA through their release of heparanase [14], preferentially from the basolateral side of endothelial cells, was shown to displace surface bound LPL from adipocytes [15]. In the current study, we report that following IL, endothelial cells demonstrate increased heparanase immunofluorescence. To evaluate whether this increased heparanase is capable of cleaving myocyte surface bound HSPG, we isolated myocytes and determined heparin releasable LPL activity. Interestingly, myocyte LPL activity following 20% IL was lower compared to CON. Whether FA can traverse from the luminal side of endothelial cells to also directly release myocyte surface-bound LPL is currently unknown. Our data suggest that similar to adipose tissue, conditions that increase circulating FA facilitate LPL translocation from the cardiac myocyte to the coronary endothelial lumen. In vivo, this mechanism likely contributes towards TG clearance.

In an effort to further validate the role of TG in the LPL translocation, two approaches were exploited. First, we terminated IL infusion to reduce plasma TG, and hearts were removed from animals after 3 h. Although normalization of peak LPL was observed, continuous heparin perfusion still released excessive LPL activity suggesting that majority of the accumulated LPL had not relocated to the luminal surface. As these animals remained hypertriglyceridemic after 3 h, we used an in vitro approach to eliminate circulating TG. Thus, following IL infusion and in vitro stripping of the enzyme with heparin, hearts were perfused for 1 h in TG-free buffer. Only IL hearts showed re-establishment of the heparin releasable peak, and on continuous perfusion of these hearts with heparin, LPL activity returned to near basal levels. Our data suggest that in the absence of TG, the accumulated enzyme pool is able to transfer to its functional location, the coronary lumen. An additional implication of this data is that the effect of IL in reducing LPL at the coronary endothelial surface is likely unrelated to the number of HSPG binding sites.

In summary, acute IL infusion augments plasma LPL, and this was associated with reduced LPL activity at the coronary lumen, but increased enzyme within endothelial cells and subendothelial space. It is likely that these effects are a consequence of FA releasing LPL from apical endothelial HSPG, in addition to augmenting endothelial heparanase, which facilitates myocyte HSPG cleavage and transfer of LPL towards the coronary lumen (Fig. 7). Should this mechanism occur globally, it could contribute towards management of hyperlipidemia.

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