Acute elevation of triglycerides increases left ventricular contractility and alters ventricular-vascular interaction

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Holland DJ, Erne D, Kostner K, Leano R, Haluska BA, Marwick TH, Sharman JE. Acute elevation of triglycerides increases left ventricular contractility and alters ventricular-vascular interaction. Am J Physiol Heart Circ Physiol 301: H123–H128, 2011. First published April 13, 2011; doi:10.1152/ajpheart.00102.2011.—Acute elevation of circulating lipids, such as the postprandial state, contributes to increased cardiovascular risk. However, the effect of acutely elevated triglycerides on arterial and left ventricular function is not completely understood. We aimed to assess whether an acute increase in triglycerides affects ventricular-vascular interaction. Fifteen healthy men (age, 49 ± 8 yr) underwent blinded, randomized infusion of saline and intravenous fat emulsion to acutely raise plasma triglycerides. All subjects underwent both randomization trials, in random order on two separate days. Ventricular-vascular interaction measures were recorded by tonometry (central blood pressure) and echocardiography (left ventricular volumes, strain, and strain rate) at baseline and after 1 h infusion. Net ventricular-vascular interaction was defined by the effective arterial elastance (Ea) to-left ventricular end-systolic elastance (Esv) ratio (Ea/Esv). When compared with saline, the infusion of intravenous fat emulsion increased triglycerides and free fatty acids (ΔP < 0.001 for both) and improved left ventricular contractility (ΔEsv, end-systolic volume and strain rate; P < 0.05 for all). However, arterial function was unchanged (ΔEa, brachial and central blood pressure; P > 0.05 for all). Overall, Esv/Ea was decreased by an infusion of intravenous fat emulsion (P = 0.004) but not saline (P > 0.05, P = 0.001 for Δ between trials). We conclude that intravenous fat emulsion and acute elevation of blood lipids (including triglycerides and free fatty acids) alter ventricular-vascular interaction by increasing left ventricular contractility without affecting arterial load. These findings may have implications for cardiovascular responses to parenteral nutrition.

left ventricle; free fatty acids

CHRONIC ELEVATION of circulating lipids is a potent risk factor for cardiovascular disease (1). Growing evidence implicates the specific role of raised triglyceride levels in the development of coronary artery disease (32, 42) and left ventricular (LV) hypertrophy (LVH) (40); however, an independent, causal relationship remains uncertain (31). Hemodynamic loading of the left ventricle varies considerably between individuals despite similar brachial blood pressure (BP) (35). This has been illustrated in patients with lipid abnormalities and increased triglycerides (49), which may help to explain the development of LVH in this population. Moreover, reports on the acute vascular response to a fatty meal or exogenous elevation of triglycerides have also demonstrated the induction of endothelial dysfunction and decreased vasoreactivity (21, 38, 44). These data suggest that repeated acute elevations of triglycerides, as occurs in the postprandial metabolic response, may contribute to increased cardiovascular risk (5, 27).

Despite the abundance of data pertaining to the risk of chronically elevated triglycerides, to our knowledge there are no data available on the combined myocardial and vascular effects in response to an acute elevation. An analysis of ventricular-vascular (V-V) interaction may be useful for assessing this response. This technique enables an analysis of the energetic efficiency of the cardiovascular system in relation to mechanical performance, specifically, how effectively the heart can transfer blood into the arterial tree while preventing extreme changes in pressure (7). Suboptimal V-V interaction may result in inefficient coupling and increased LV load, a scenario often apparent in hypertension and heart failure (3, 6, 7, 12). Considering the widely reported adverse effects associated with the postprandial response, we hypothesized that an acute elevation of serum triglycerides would increase large artery stiffness, raise central BP, and impair V-V interaction.

METHODS

Patient selection. Fifteen healthy men aged 30–65 yr and free of cardiac or metabolic medications were recruited by local advertisement. No subject had a history of coronary artery disease; diabetes mellitus; LVH (>131 g/m²) (18); aortic valve stenosis; gastric or duodenal ulcers; or disease of the liver, pancreas, or kidney. This study complied with the declaration of Helsinki and was approved by the local Human Research Ethics Committee. All patients gave informed consent before their involvement in the study.

Study protocol. This crossover study was conducted in a randomized, double-blind fashion. All operators (and subjects) were blinded to the randomization allocation during data acquisition and analysis. Subjects attended the laboratory after an overnight fast (>9 h, water allowed) on two separate occasions, separated by approximately 1 wk. After a minimum of 10 min supine rest in a temperature-controlled room, an intravenous cannula was inserted in an antecubital vein in both arms for the infusion (right arm) and collection (left arm) of blood samples. The cannula used for substrate infusion was connected to a control tap to allow for constant saline-heparin infusion along with the randomization solution. Immediately, after baseline blood collection, a saline infusion was initiated and after 10 min (rate, 90 ml/h), baseline measurements of regional arterial stiffness (pulse-wave velocity; PWV), central BP, and echocardiography were recorded. Following the completion of baseline measurements, a 500-ml bolus of heparin (in saline solution) was given to activate lipoprotein lipase (50). At the initial visit, patients were randomly assigned to receive either saline or an intravenous fat emulsion (IFE; intralipid, 20%). The alternate randomization option was prescribed...
during the second appointment. The infusion rate for both random-
ization trials was 90 ml/h and was maintained for 60 min. After 60 
min, a postinfusion blood sample was drawn and PWV, central BP, 
and echocardiography were repeated with the infusion maintained 
until the completion of data acquisition. All measurements were 
performed by a technician blinded to the randomization group.

Biochemistry. Venous blood was sampled at baseline and after 60 
min of infusion. Whole blood was collected in lithium heparin (gel) 
and EDTA tubes for a full assessment of serum electrolytes and 
glucose and liver function as per standard hospital laboratory proce-
dures. A full lipid profile analysis was performed using a standard 
clinical pathology system (SYNCHRON LX System, Beckman 
Coulter, CA). Cholesterol levels were determined by direct quantita-
tive determination. In brief, this method employs a unique detergent to 
solubilize only the parameter of interest, i.e., HDL, LDL, and very 
low-density lipoprotein (VLDL) while inhibiting the reaction with 
other cholesterol enzymes. Specific reagents are then used to measure 
cholesterol concentration by timed end-point methods, monitoring the 
change in absorbance at various wavelengths, which is directly pro-
portional to the change in cholesterol concentration. Circulating free 
fatty acid (FFA) concentrations were also measured from frozen 
samples (−70°C) using a standard clinical system (VITROS 5.1 FS 
Chemistry System, Ortho-Clinical Diagnostics).

Vascular function. Arterial waveforms were acquired in duplicate 
at the radial artery by handheld applanation tonometry. All waveforms 
were calibrated to brachial BP measured in duplicate immediately 
before waveform acquisition by a semiautomated BP monitor (52000, 
Welch-Allen). The central pressure waveform was derived from the 
radial pulse using a generalized transfer function and commercial 
software (SphygmoCor, AtCor Medical, Sydney, Australia). This 
technique is valid (9, 33) and reliable (15, 47) for the measurement of 
central (aortic) waveform characteristics, including central BP. Aug-
mented pressure was measured as the difference between P1 and P2 
on the central pressure waveform, with the augmentation index 
representing the augmented pressure as a percentage of total central 
pulse pressure. End-systolic pressure (ESP) was calculated as the 
pressure at the nadir of the diastolic notch on the central pressure 
waveform. Arterial stiffness was estimated by duplicate measures of 
aortic and brachial PWV. These were acquired with ECG-gated 
sequential tonometry at the carotid, radial, and femoral arterial sites as 
previously described (47). Peripheral vascular resistance was calcu-
lated by mean arterial pressure/cardiac output and expressed in pe-
ripheral resistance units (24).

Echocardiography. Transthoracic echocardiography was performed on 
all patients pre- and postinfusion. A standard echocardiography ma-
chine was used for all measurements (Vivid 9; GE Medical Systems) 
with a 2.5-MHz transducer. Images were stored on optical disc for 
offline analysis by a blinded technician. A diastolic assessment was 
performed with a 2.5-MHz transducer. Images were stored on optical disc for 
all patients pre- and postinfusion. A standard echocardiography ma-
chine was used for all measurements (Vivid 9; GE Medical Systems)

RESULTS

The study population was reported with a healthy mean 
age of 49 ± 8 yr (range, 34 to 61 yr), with a mean body mass 
index of 25.6 ± 3.2 kg/m² and resting systolic BP of 116 ± 10 
mmHg (Tables 1 and 2). All subjects were followed up 24 h 
after both visits, and no adverse reactions were reported. There 
were no preinfusion (i.e., baseline) differences between visits 
for any variable (P > 0.05 for all).

Biochemistry. Baseline triglycerides and FFAs were within the 
normal range (Table 1). For individual trials, the infusion of the 
IFE solution resulted in a significant increase in triglycerides 
(P < 0.001), whereas there was a decrease after saline 
(P < 0.001). Despite an increase in circulating FFAs in both IFE 
(P = 0.001) and saline (P = 0.004) trials, the increment was 
significantly greater in patients receiving the IFE (ΔP < 0.001). There was no change in total cholesterol in either group, 
despite a significant decrease in LDL and an increase in 
VLDL cholesterol compared with the saline infusion (ΔP < 0.001 for both). The change (i.e., Δ) in hemoglobin (P = 0.043), platelets (P = 0.011), and eosinophils (P = 0.001) was 
significantly greater after IFE compared with saline. There 
were no between-group changes in red cell count, mean cell 
volume, white cell count, neutrophils, lymphocytes, mono-
cytes, or basophils (ΔP > 0.05 for all). There was no statistical 
change in glucose between trials.

Vascular response. There were no preinfusion differences in 
arterial stiffness or arterial waveform characteristics between 
visits (P > 0.05 for all; Table 2). When compared with saline, 
IFE infusion resulted in no significant changes for any BP 
variable (ΔP > 0.05 for all), with the exception of the aug-
mentation index at 75 beats/min (ΔP = 0.015). There were no

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associations between the lipid response to IFE (i.e., Δ triglycerides, FFAs) and BP variables (P > 0.05 for all), and there was no difference in peripheral vascular resistance between trials (ΔP > 0.05 for all).

Myocardial response. Table 2 also displays myocardial function in response to infusion. LV contractility was enhanced in response to IFE, signified by an increased E\textsubscript{LV} (ΔP = 0.006) and a decreased mean ESV (ΔP = 0.007; Table 2). This

Table 2. Vascular and left ventricular function in response to infusion with saline and intravenous fat emulsion

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Postinfusion</th>
<th>ΔP Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td></td>
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<tr>
<td>Brachial SBP, mmHg</td>
<td>115 ± 8</td>
<td>116 ± 8</td>
<td>0.05</td>
</tr>
<tr>
<td>Brachial DBP, mmHg</td>
<td>71 ± 9</td>
<td>72 ± 6</td>
<td>0.75</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>85 ± 10</td>
<td>87 ± 8</td>
<td>0.001</td>
</tr>
<tr>
<td>Brachial PP, mmHg</td>
<td>44 ± 3</td>
<td>44 ± 4</td>
<td>0.01</td>
</tr>
<tr>
<td>Central SBP, mmHg</td>
<td>104 ± 11</td>
<td>107 ± 9</td>
<td>0.61</td>
</tr>
<tr>
<td>Central DBP, mmHg</td>
<td>72 ± 9</td>
<td>73 ± 7</td>
<td>0.16</td>
</tr>
<tr>
<td>Central PP, mmHg</td>
<td>33 ± 3</td>
<td>34 ± 3</td>
<td>0.05</td>
</tr>
<tr>
<td>AIx, %</td>
<td>17.2 ± 10.6</td>
<td>21.2 ± 12.2</td>
<td>0.05</td>
</tr>
<tr>
<td>AIx (at 75 beats/min), %</td>
<td>7.1 ± 12.8</td>
<td>9.2 ± 14.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>54 ± 8</td>
<td>51 ± 7</td>
<td>0.65</td>
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<tr>
<td>Cardiac output, l/min</td>
<td>3.4 ± 0.5</td>
<td>3.3 ± 0.6</td>
<td>0.17</td>
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<tr>
<td>Peripheral vascular resistance, PRU</td>
<td>25.8 ± 6.2</td>
<td>27.7 ± 6.9</td>
<td>0.12</td>
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<tr>
<td>Pulse wave velocity</td>
<td></td>
<td></td>
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<tr>
<td>Aortic, m/s</td>
<td>6.7 ± 0.9</td>
<td>6.8 ± 0.6</td>
<td>0.46</td>
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<tr>
<td>Brachial, m/s</td>
<td>8.0 ± 8.5</td>
<td>8.5 ± 8.0</td>
<td>0.29</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
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<tr>
<td>E velocity, cm/s</td>
<td>0.62 ± 0.12</td>
<td>0.65 ± 0.13</td>
<td>0.59</td>
</tr>
<tr>
<td>A velocity, cm/s</td>
<td>0.45 ± 0.12</td>
<td>0.44 ± 0.09</td>
<td>0.81</td>
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<tr>
<td>E/A ratio</td>
<td>1.44 ± 0.31</td>
<td>1.52 ± 0.48</td>
<td>0.89</td>
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<tr>
<td>Deceleration time, ms</td>
<td>214 ± 36</td>
<td>204 ± 32</td>
<td>0.31</td>
</tr>
<tr>
<td>s', m/s</td>
<td>0.07 ± 0.01</td>
<td>0.07 ± 0.01</td>
<td>0.37</td>
</tr>
<tr>
<td>e', m/s</td>
<td>0.09 ± 0.02</td>
<td>0.08 ± 0.01</td>
<td>0.62</td>
</tr>
<tr>
<td>a', m/s</td>
<td>0.09 ± 0.02</td>
<td>0.09 ± 0.02</td>
<td>0.58</td>
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<tr>
<td>E/e</td>
<td>7.2 ± 1.9</td>
<td>7.9 ± 1.8</td>
<td>0.81</td>
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<tr>
<td>ESV, ml</td>
<td>37 ± 11</td>
<td>40 ± 14</td>
<td>0.07</td>
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<tr>
<td>EDV, ml</td>
<td>102 ± 25</td>
<td>106 ± 28</td>
<td>0.26</td>
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<tr>
<td>Ejection fraction, %</td>
<td>64 ± 5</td>
<td>66 ± 6</td>
<td>0.001</td>
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<tr>
<td>Global strain, %</td>
<td>−19.37 ± 1.64</td>
<td>−19.56 ± 2.09</td>
<td>0.91</td>
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<tr>
<td>Global strain rate, s\textsuperscript{−1}</td>
<td>−1.05 ± 0.11</td>
<td>−1.07 ± 0.09</td>
<td>0.011</td>
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<tr>
<td>Pressure-volume relationship</td>
<td></td>
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<tr>
<td>E\textsubscript{L}, mmHg/ml</td>
<td>1.55 ± 0.44</td>
<td>1.57 ± 0.4</td>
<td>0.19</td>
</tr>
<tr>
<td>E\textsubscript{LV}, mmHg/ml</td>
<td>2.89 ± 1.27</td>
<td>2.78 ± 1.28</td>
<td>0.006</td>
</tr>
<tr>
<td>E\textsubscript{LV}/E\textsubscript{L}</td>
<td>0.37 ± 0.12</td>
<td>0.61 ± 0.13</td>
<td>0.001</td>
</tr>
<tr>
<td>SW, mmHg/ml</td>
<td>6.186 ± 589</td>
<td>6.306 ± 1.137</td>
<td>0.210</td>
</tr>
<tr>
<td>PVA, mmHg/ml</td>
<td>7.763 ± 1,176</td>
<td>8.238 ± 1,609</td>
<td>0.789</td>
</tr>
</tbody>
</table>

Values are means ± SD; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; AIx, augmentation index; PRU, peripheral resistance units; s', e', and a' myocardial velocities in systole and early and late diastole, respectively; ESV, end-systolic volume; EDV, end-diastolic volume; E\textsubscript{A}, arterial elastance; E\textsubscript{LV}, left ventricular end-systolic elastance; SW, stroke work; PVA, pressure-volume area (area under the pressure-volume curve). There were no significant preinfusion differences between visits for any variable (P > 0.05 for all). Note: ΔP value is for the change between trials from preinfusion to postinfusion (paired samples t-test).
finding was also supported by an improvement in ejection fraction ($P = 0.001$), global two-dimensional SR ($P = 0.011$), and strain ($P = 0.005$) after IFE. Importantly, the change in these variables from pre- to postinfusion were significantly greater that the saline group ($\Delta P < 0.05$ for all; Fig. 1A) with the exception of global strain ($\Delta P = 0.091$). There were no significant changes in indexes of diastolic function with IFE ($\Delta P > 0.05$ for all).

V-V response. Noninvasive LV pressure-volume loops were used to assess the interaction between the left ventricle and the arterial system. These data are presented in Table 2 and Fig. 1B. Despite the aforementioned increase in $E_{LV}$ after the IFE infusion, there was no effect on $E_A$, either within or between trials ($P > 0.05$ for all). As a result of increased $E_{LV}$, IFE resulted in a significant decrease in the $E_A/E_{LV}$ compared with saline ($\Delta P = 0.001$). Whereas there were no associations between the changes in triglyceride or FFA concentration with indexes of V-V interaction after IFE, the change in LDL cholesterol was inversely associated with the changes in $E_{LV}$ ($r = -0.647; P = 0.012$) and $E_A/E_{LV}$ ($r = 0.742, P = 0.002$).

The change in VLDL cholesterol held similar associations with $E_A/E_{LV}$ ($r = -0.637; P = 0.014$). Importantly, there were also associations between the changes in V-V interaction and global SR with IFE, $E_A$ ($r = 0.732; P = 0.004$), and stroke work/PVA ($r = -0.658; P = 0.015$), which were not apparent with saline.

**DISCUSSION**

We hypothesized that an acute elevation of circulating triglycerides would have adverse effects on arterial stiffness, central BP, and V-V interaction. On the contrary, we found increased LV contractility with the infusion of an IFE as evidenced by an increase in $E_{LV}$ and a decrease in ESV, in addition to an enhancement of global SR. There was a reduction of $E_A/E_{LV}$ (i.e., net V-V interaction), but there was no significant change in arterial function ($E_A$, brachial and central BP) between the trials, indicating that the changes in contractility occurred independent of LV loading. Overall, the results suggest an acute increase in myocardial contractility, independent of $E_A$ and BP variables.

Postprandial lipemia induces a number of vasculature changes that may augment cardiovascular risk (2). Acute changes in vascular function perturb V-V interaction and overall cardiovascular performance. Raised triglycerides in cases such as the metabolic syndrome may, therefore, present a causative link to cardiovascular risk. This study employed an acute model of raised triglycerides (and FFAs) with an IFE, similar to postprandial studies after high-fat meals (28), but found improvements in LV contractility, independent of arterial function. We speculate that similar findings may occur in the postprandial response to high-fat meals, but studies will need to be conducted to confirm this given that our model was infusion based, and this is not the same as eating a meal where hormonal responses may be different. The rationale for this approach was an attempt to study the isolated effect of raised triglycerides and exclude the potential hormonal influence of food ingestion on the cardiac and vascular response. These results suggest differences between an acute and chronic elevation of triglycerides. A previous observational study in patients with chronically raised triglycerides reported increased arterial stiffness and raised central, but not brachial, BP (49). It appears these adverse changes were more related to LDL cholesterol; however, these investigators did not assess V-V coupling, and other studies suggest that increased arterial stiffness may impair V-V interaction through augmented cardiac work (16).

Infusion of heparin with triglyceride emulsion activates lipoprotein lipase (50), providing a rich source of FFAs. An acute increase in circulating FFAs alters myocardial substrate uptake (19, 20, 30), and this shift in metabolism increases oxygen demand (i.e., decrease myocardial efficiency) for a given workload (22). Whereas increased oxygen uptake may reflect a decrease in efficiency, the current study supports previous work (25), suggesting that overall cardiac work is increased with increasing FFA availability. This concept has been demonstrated in a close-chest animal model, where myocardial oxygen uptake increased in response to an infusion of heparin and triglyceride emulsion, despite no change in mechanical power or myocardial blood flow (22). Other animal studies suggest that increased FFA supply to the myocardium may result in isolated diastolic dysfunction with no effect on

Fig. 1. A: percent change in myocardial function (i.e., contractility) from preinfusion to postinfusion for saline and intravenous fat emulsion (IFE). LV, left ventricular; EF, ejection fraction; SR, strain rate; ESV, end-systolic volume. Note: absolute change displayed for LV EF. B: percent change in ventricular-vascular interaction from preinfusion to postinfusion for saline and IFE. $E_A$, arterial elastance; $E_{LV}$, LV elastance; $E_A/E_{LV}$, ratio of $E_A$ to $E_{LV}$ (i.e., net ventricular-vascular interaction).
systolic function (10, 11, 13). Cardiac studies in humans appear to support previous findings in animal models. A previous study by Pacold et al. (25) demonstrated a reduction in LV performance (though only quantified by the LV ejection fraction) with triglyceride infusion, followed by an improvement in LV function after the administration of heparin to increase FFAs. Similarly, an active model of FFA depletion demonstrated a reduction of myocardial FFA uptake, resulting in a depression of cardiac work (43). The stimulation of the cardiac autonomic nervous system and the elevation of plasma catecholamines is a possible mediator of the change in myocardial function (26). While this study did not undertake a formal assessment of these pathways, hypertriglyceridemia is associated with increased circulating FFAs and sympathetic overactivity (14).

While the significance of decreased $E_A/E_{LV}$ (despite being within the normal range) is unclear, the findings from this study may have clinical implications. In the critical care setting, IFE has been successfully employed as an antidote to various forms of cardiotoxicity induced by lipid-soluble drugs. Though the mechanism of action remains unclear, there are two theories. The first is a reduction of free drug concentration through the binding of fat emulsion to lipophilic compounds (i.e., a lipid sink) (45) and enhanced hepatic clearance (41). Second, IFE may assist in maintaining myocardial homeostasis through increased LV contractility (4). This acts to increase circulating FFA concentrations and augment substrate delivery to the starving myocardium, thus shifting myocardial metabolism to favor this substrate (4, 41, 46). The findings of the current study may support the use of IFE in the critical care setting, demonstrating an improvement in LV systolic function, independent of changes in LV loading.

This study was performed in low-risk men of a wide age range and has some limitations. We recruited low-risk males to limit the probability of undiagnosed cardiovascular disease. As such, the results from this study may not apply to patients with known cardiovascular disease, such as heart failure. In addition, while all resting echocardiograms were normal with no LV wall motion abnormalities, we did not undertake formal exercise testing to screen for inducible ischemia. Since these subjects were healthy and did not require invasive catheterization procedures, our assessment of V-V interaction was based on noninvasive techniques. While these have been validated (7), the tests would not be expected to be as accurate as invasive methods. While we did not find changes in peripheral vascular resistance, cardiac output, or arterial function by applanation tonometry, we cannot exclude the regional vaso-motor response from arterial beds such as the muscular, splanchnic, or renal vasculature. Furthermore, the use of healthy controls prevents an extrapolation of these results to patients with established hypertriglyceridemia, in whom a greater response to IFE seems plausible. While FFAs and triglycerides were measured at similar times, we did not undertake formal protocols to prevent lipolysis ex vivo, and this may have affected our results. The results from this study suggest that the acute effects of increased circulating triglycerides may have very different effects compared with the chronic setting, such as potential vasoconstriction and increased BP with longer exposure to raised lipids (26, 29). However, this is only speculation, since the current study investigated the acute but not chronic response to IFE. Unlike prior studies that directly assessed endothelial function, we did not undertake these formally but assessed large artery stiffness, central BP, and V-V interaction in response to a lipid infusion.

Conclusions. This study demonstrates the effect of an acute administration of IFE on V-V interaction in healthy males. When compared with a control saline infusion, IFE increased myocardial contractility, an effect demonstrated by changes in V-V interaction and myocardial function by echocardiography, independent of LV load and arterial function. These results suggest differing effects of an acute versus chronic elevation of blood lipids on LV function and may provide support for the use of IFE infusions in the management of complications associated with lipid-soluble drugs.

GRANTS

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DISCLOSURES

J. E. Sharman has research collaborations with AtCor Medical.

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