Impact of aging on myocardial metabolic response to dobutamine

Pablo F. Soto,1 Pilar Herrero,2 Andrew M. Kates,1 Carmen S. Dence,2 Ali A. Ehsani,1 Victor Dávila-Román,1 Kenneth B. Schechtman,3 and Robert J. Gropler1,2


Soto, Pablo F., Pilar Herrero, Andrew M. Kates, Carmen S. Dence, Ali A. Ehsani, Victor Dávila-Román, Kenneth B. Schechtman, and Robert J. Gropler. Impact of aging on myocardial metabolic response to dobutamine. Am J Physiol Heart Circ Physiol 285: H2158–H2164, 2003. First published July 24, 2003; 10.1152/ajpheart.00086.2003. —In humans, under resting conditions there is an age-related decrease in myocardial fatty acid utilization (MFAU) and oxidation (MFAO) and a relative increase in myocardial glucose utilization (MGU). The impact of age on an individual’s myocardial metabolic response to catecholamines is not well defined. Sixteen younger (mean age, 26 ± 5 yr) and 14 older (mean age, 69 ± 4 yr) volunteers underwent positron emission tomography to measure myocardial blood flow, myocardial oxygen consumption (MV\textsubscript{O}\textsubscript{2}), MFAU, MFAO, and MGU both under resting conditions and during dobutamine infusion. In response to dobutamine administration, the rate-pressure product, myocardial blood flow, and MV\textsubscript{O}\textsubscript{2} measurements increased by similar amounts in both groups. No age-related differences were noted in the responses of plasma insulin, glucose, fatty acid, or lactate levels to dobutamine. With dobutamine infusion, MFAU and MFAO increased by a similar extent in both younger and older volunteers (age/dobutamine interactions, P = 0.62 and 0.75, respectively). In contrast, MGU increased with dobutamine administration in the younger (from 149 ± 71 to 209 ± 78 nmol·g\textsuperscript{-1}·min\textsuperscript{-1}, P = 0.04) but not in the older (from 235 ± 147 to 178 ± 84 nmol·g\textsuperscript{-1}·min\textsuperscript{-1}, P = 0.23; age/dobutamine interaction, P = 0.03) group. With dobutamine infusion, hearts in both younger and older volunteers responded by increasing their MFAU and MFAO values. Whereas younger hearts also responded with an increase in MGU, older hearts did not. Although the clinical significance of these findings awaits further study, these results may partially explain the impaired contractile reserve and the increased incidence of cardiovascular disease in older individuals.

fatty acids; glucose; oxidation; heart; catecholamine

CARDIOVASCULAR DISEASE is a primary cause of death and disability in Americans 65 yr of age or older (2). The prevalence of a variety of cardiac disorders including atherosclerosis, atrial fibrillation, heart failure, and hypertension increases with age (1). Moreover, because of the effects of aging on the heart, the clinical manifestations of these disorders are more pronounced in older patients than in younger ones. Consequently, it is important to better delineate the effects of aging on the heart to potentially reduce both the incidence and the impact of various disorders that are specific to the cardiovascular system. Aging has numerous deleterious effects on the heart. For example, with increasing age there is impairment in left ventricular systolic reserve capacity and in diastolic filling (34) as well as blunted inotropic and chronotropic responses to certain ß-adrenergic agonists (26). A decline in myocardial vasodilator capacity, predominantly through endothelial-dependent mechanisms that are distinct from epicardial involvement by coronary atherosclerosis, is present in both experimental models of aging and in older humans (3, 9, 12, 14, 22, 32). Similarly, there are age-related effects on myocardial substrate metabolism. Using positron emission tomography (PET), we have recently shown that with increasing age there is an absolute decline in myocardial fatty acid utilization (MFAU) and oxidation (MFAO) and a relative increase in myocardial glucose utilization (MGU) under resting conditions (23). However, it is not known whether increasing age alters the myocardial metabolic response to catecholamines. Although the response of myocardial fatty acid and glucose metabolism to catecholamines has been characterized extensively in experimental animals, this response is less clear in humans (13, 17, 20). Accordingly, the aims of this study were 1) to determine the changes in myocardial fatty acid and glucose metabolism in response to dobutamine infusion as measured by PET in humans, and 2) to identify any difference in the myocardial metabolic response between healthy younger and older adults.

METHODS

Study Population

We studied 16 younger sedentary, healthy volunteers (mean age, 26 ± 5 yr; 5 men and 11 women) and 14 older...
sedentary, healthy volunteers (mean age, 69 ± 4 yr; 9 men and 6 women). Some data were obtained from a subgroup of volunteers that were used previously to characterize age-related effects on resting myocardial substrate metabolism (23). All volunteers were normotensive nonsmokers who had no family history for coronary artery disease. Individuals with insulin resistance and impaired glucose tolerance were excluded by a normal oral glucose tolerance test and a normal plasma insulin assay. Individuals with hyperlipidemia were excluded by a normal fasting plasma lipid profile. No volunteer was taking any medication at the time of the study.

All volunteers had a normal physical exam and a normal rest-exercise echocardiogram. Both the younger and older volunteers exhibited normal resting left ventricular ejection fraction measurements as quantified by echocardiography (65 ± 7 and 66 ± 6%, respectively; P = not significant). Left ventricular mass indexes were normal in both younger and older volunteers (younger, 74 ± 14 and older, 83 ± 10 g/m²), although the value was slightly higher in the older volunteers (P = 0.05). The study was approved by the Human Studies and Radioactive Drug Research Committees at the Washington University School of Medicine. Written informed consent was obtained from all volunteers before enrollment in the study.

**Imaging Protocol**

All studies were performed with a conventional commercially available tomograph (Siemens ECAT 962 HR+, Siemens Medical Systems; Iselin, NJ). All volunteers were studied after an overnight fast. Heart rate and rhythm as well as blood pressure values were measured at regular intervals throughout the study. The rate-pressure product (RPP) was used as an index of myocardial work and oxygen demand (6). RPP was calculated from the mean systolic blood pressure and the mean heart rate measurements obtained throughout the course of a single PET study. PET was used to measure myocardial blood flow (MBF) with [15O]water, myocardial oxygen consumption (MVO₂) was measured with [11C]acetate, MFAU and MFAO were measured with [11C]palmitate, and MGU was measured with [11C]glucose. During the study, venous blood samples were obtained at predetermined intervals to measure plasma substrate (glucose, fatty acids, No lactate and insulin levels. In addition, plasma levels of [13C]CO₂ and [13C]lactate were measured to correct the arterial input function during compartmental modeling of the myocardial kinetics of the various metabolic tracers (see below). All volunteers underwent the study protocol on two separate days. Day 1 measurements were obtained with volunteers under resting conditions, whereas on day 2, measurements were repeated during the intravenous administration of dobutamine at an infusion rate of 10 μg·kg⁻¹·min⁻¹.

**Image Analysis**


The mean plasma glucose, fatty acid, lactate, and insulin levels averaged over a single imaging study both at rest and during dobutamine infusion for the...
Hemodynamics, MBF, and \( \text{MV}_{\text{O}_2} \)

Hemodynamics, MBF, and \( \text{MV}_{\text{O}_2} \) measurements are summarized in Table 2. Heart rates did not differ between the groups at rest; however, during dobutamine infusion, heart rates trended higher in the older volunteers (\( P = 0.07 \)). As such, the heart rate response to dobutamine infusion was greater in older volunteers compared with the younger ones (\( P < 0.008 \) for the age/dobutamine interaction). Systolic blood pressure at rest was higher in the older group (\( P < 0.05 \)) but was similar in the two groups during dobutamine infusion. Consequently, the increase in systolic blood pressure with dobutamine infusion was greater in the younger group (\( P < 0.0001 \) for the age/dobutamine interaction). At rest, diastolic blood pressure was higher in older volunteers compared with younger ones (\( P < 0.05 \)). In contrast, during dobutamine infusion, diastolic blood pressure was lower in the older group compared to the younger group (\( P < 0.05 \)). Moreover, whereas diastolic blood pressure increased in the younger group during dobutamine infusion, it declined in the older group (\( P < 0.05 \) compared with rest, and \( P < 0.0001 \) for the age/dobutamine interaction). Although the RPP was higher in the older volunteers compared with the younger group at rest, it did not differ between the groups during dobutamine infusion. The increase in the RPP in response to dobutamine infusion was similar between the groups. Values for MBF and \( \text{MV}_{\text{O}_2} \) were similar between the groups both at rest and during dobutamine infusion. Moreover, the increase in MBF and \( \text{MV}_{\text{O}_2} \) in response to dobutamine infusion was similar between the groups. The RPP/\( \text{MV}_{\text{O}_2} \) rela-
INTERVENTION

Table 3. Myocardial fatty acid metabolism

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<tr>
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<th>Younger Controls</th>
<th>Older Volunteers</th>
<th>Age/Dob Interaction, P</th>
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<tr>
<td></td>
<td>Rest</td>
<td>Dob</td>
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<tr>
<td>MFAU, nmol·g⁻¹·min⁻¹</td>
<td>212 ± 58</td>
<td>427 ± 145*</td>
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<tr>
<td>MFAO, nmol·g⁻¹·min⁻¹</td>
<td>205 ± 58</td>
<td>413 ± 144*</td>
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<tr>
<td>%MFAO, MFAO/MFAU</td>
<td>94 ± 7</td>
<td>94 ± 7</td>
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<tr>
<td>MFAU/MVO₂, nmol FFA/μmol O₂</td>
<td>48 ± 19</td>
<td>42 ± 17</td>
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<tr>
<td>MFAO/MVO₂, nmol FFA/μmol O₂</td>
<td>47 ± 19</td>
<td>42 ± 17</td>
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Values are means ± SD. MFAU, myocardial fatty acid utilization; MFAO, myocardial fatty acid oxidation. *P < 0.05 vs. corresponding rest value; †P < 0.05 vs. corresponding value for young controls.

Myocardial Fatty Acid Metabolism

The results of measurements of myocardial fatty acid metabolism with and without correction for MVO₂ are shown in Table 3. The level of MFAU was similar between the younger and older groups at rest and during dobutamine infusion. In response to dobutamine infusion, MFAU increased to a similar extent in both groups, which parallels the similar increase in plasma FFAs (see Table 1). At baseline, MFAO was lower in the older group compared with the younger group (P = 0.04). With dobutamine infusion, MFAO values were also similar between younger and older volunteers. The increase in MFAO in response to dobutamine infusion was similar between the two groups. The %MFAO reflects the fraction of extracted palmitate that was oxidized. At rest, this level was lower in the older group but was similar during dobutamine infusion without resulting age/dobutamine interaction. MFAU/MVO₂ was not demonstrably different between younger and older hearts either at rest or with dobutamine infusion. At rest, MFAO/MVO₂ was lower in the older group but did not differ between the two groups with dobutamine infusion. Moreover, MFAU/MVO₂ and MFAO/MVO₂ did not increase in either group with dobutamine infusion, which suggests that the increase in myocardial fatty acid metabolism was commensurate with the increase in MVO₂.

Myocardial Glucose Metabolism

The results of the measurements of myocardial glucose metabolism with and without correction for MVO₂ are shown in Table 4. At rest, MGU was higher in older volunteers compared with the younger group. The level of MGU increased with dobutamine infusion in younger individuals (P < 0.05) but not in older volunteers (P = 0.03 for the age/dobutamine interaction). After correction for MVO₂, there was a similar decline in MGU to dobutamine infusion in both younger and older individuals.

DISCUSSION

The results of this study are the first to demonstrate that in human myocardium, β-adrenergic stimulation results in an increase in MFAU and MFAO. Furthermore, these increases are commensurate with the resultant increase in MVO₂. These findings are similar in younger and older individuals. In contrast to MFAU, MGU values corrected for MVO₂ declined in both younger and older individuals in response to dobutamine infusion. The magnitude of this decline was similar between the two groups. In contrast with younger individuals, however, older individuals did not experience a change in MGU level in response to dobutamine administration.

Hemodynamic Responses to Dobutamine

Older volunteers demonstrated an increased chronotropic response to dobutamine vs. younger volunteers. This is consistent with the results of an earlier study that showed that in contrast to the decreased heart rate response in the elderly that was seen with isoprenaline administration, there was an increased sensitivity to dobutamine-induced tachycardia in older individuals (29). Furthermore, the observed decline in diastolic blood pressure observed in the older volun-

Table 4. Myocardial glucose metabolism

<table>
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<td></td>
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<tr>
<td>MGU, nmol·g⁻¹·min⁻¹</td>
<td>149 ± 71</td>
<td>209 ± 78*</td>
<td></td>
</tr>
<tr>
<td>MGU/MVO₂, nmol glucose/μmol O₂</td>
<td>36 ± 23</td>
<td>20 ± 9*</td>
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Values are means ± SD. MGU, myocardial glucose utilization. *P < 0.05 vs. corresponding rest value; †P < 0.05 vs. corresponding value for young controls.
EFFECTS OF AGE AND DOBUTAMINE ON MYOCARDIAL METABOLISM

The effects of age and dobutamine on myocardial metabolism have been studied primarily in experimental animals (10, 17, 20). Moreover, the pattern in myocardial substrate metabolism that was observed was dependent upon the experimental model used. For example, in isolated working rat hearts, \( \alpha \)-adrenergic stimulation with epinephrine resulted in an initial burst of glycolysis followed by an increase in myocardial glucose uptake and ultimately glucose oxidation. The observed increase in glucose oxidation in this model was nearly 14-fold. In addition, lactate release increased by nearly 10-fold, primarily from the glycolysis of extracted glucose. In contrast, the oxidation of FFAs (in the form of oleate oxidation) only increased slightly with the administration of epinephrine. Thus in this model, catecholamine stimulation resulted in augmentation of glucose metabolism and not fatty acid metabolism (17). In contrast, in an open-chest swine model, the administration of dobutamine at 15 \( \mu \)g·g\(^{-1}\)·min\(^{-1}\) resulted in a 248% increase in MGU and a 210% increase in MFAU values (19). In addition, lactate uptake was increased by 149%. Measurements of glucose and fatty acid oxidation were not performed. The increase in MFAU was associated with a decrease in the level of malonyl CoA, an enzyme responsible for inhibiting carnitine palmitoyltransferase I. Thus the decrease in malonyl CoA likely caused an increase in MFAO (19). The contrasting responses in myocardial fatty acid metabolism to catecholamine stimulation in these models can likely be explained by the lipolytic effects of \( \beta \)-adrenergic stimulation in peripheral adipose tissue via hormone-sensitive lipase (30). In vivo peripheral lipolysis will increase plasma fatty acid levels, which, when combined with the increase in MBF, will increase fatty acid delivery to the heart and thus increase MFAU and MFAO. Thus in the isolated perfused heart, the infusion of catecholamines does not change fatty acid delivery (because of the lack of the peripheral lipolytic effect and stable blood flow), and as a consequence, MFAU and MFAO do not increase. The results of the present study confirm these observations (see Table 3) and are in agreement with an earlier study in humans (33) that demonstrated increased myocardial fatty acid uptake based on arterial coronary sinus differences in response to isoproterenol (a primarily \( \beta \)-agonist). In contrast, catecholamines have direct stimulatory effects on myocardial glucose uptake and oxidation. For example, \( \alpha \)-adrenergic stimulation has been shown to increase MGU through a variety of mechanisms including cAMP and cAMP-dependent protein kinase, increased Ca\(^{2+}\) transients, and the phosphatidylinositol 3-kinase-dependent pathway. In addition, \( \alpha \)-adrenergic stimulation promotes translocation of glucose transporter 4 and thus glucose transport (13). These effects are in addition to \( \beta \)-adrenergic stimulation of insulin release and the subsequent increase in myocardial glucose uptake due to increased plasma insulin levels (18). In the present study, the observed increase in MGU in the younger control group supports the premise that a direct effect on myocardial glucose uptake by dobutamine occurs in humans (see Table 4).

Normal Myocardial Metabolic Response to Catecholamines

To date, the changes in myocardial glucose and fatty acid metabolism in response to catecholamine stimulation have been studied primarily in experimental animals (10, 17, 20). Moreover, the pattern in myocardial substrate metabolism that was observed was dependent upon the experimental model used. For example, in isolated working rat hearts, \( \alpha \)-adrenergic stimulation with epinephrine resulted in an initial burst of glycolysis followed by an increase in myocardial glucose uptake and ultimately glucose oxidation. The observed increase in glucose oxidation in this model was nearly 14-fold. In addition, lactate release increased by nearly 10-fold, primarily from the glycolysis of extracted glucose. In contrast, the oxidation of FFAs (in the form of oleate oxidation) only increased slightly with the administration of epinephrine. Thus in this model, catecholamine stimulation resulted in augmentation of glucose metabolism and not fatty acid metabolism (17). In contrast, in an open-chest swine model, the administration of dobutamine at 15 \( \mu \)g·g\(^{-1}\)·min\(^{-1}\) resulted in a 248% increase in MGU and a 210% increase in MFAU values (19). In addition, lactate uptake was increased by 149%. Measurements of glucose and fatty acid oxidation were not performed. The increase in MFAU was associated with a decrease in the level of malonyl CoA, an enzyme responsible for inhibiting carnitine palmitoyltransferase I. Thus the decrease in malonyl CoA likely caused an increase in MFAO (19). The contrasting responses in myocardial fatty acid metabolism to catecholamine stimulation in these models can likely be explained by the lipolytic effects of \( \beta \)-adrenergic stimulation in peripheral adipose tissue via hormone-sensitive lipase (30). In vivo peripheral lipolysis will increase plasma fatty acid levels, which, when combined with the increase in MBF, will increase fatty acid delivery to the heart and thus increase MFAU and MFAO. Thus in the isolated perfused heart, the infusion of catecholamines does not change fatty acid delivery (because of the lack of the peripheral lipolytic effect and stable blood flow), and as a consequence, MFAU and MFAO do not increase. The results of the present study confirm these observations (see Table 3) and are in agreement with an earlier study in humans (33) that demonstrated increased myocardial fatty acid uptake based on arterial coronary sinus differences in response to isoproterenol (a primarily \( \beta \)-agonist). In contrast, catecholamines have direct stimulatory effects on myocardial glucose uptake and oxidation. For example, \( \alpha \)-adrenergic stimulation has been shown to increase MGU through a variety of mechanisms including cAMP and cAMP-dependent protein kinase, increased Ca\(^{2+}\) transients, and the phosphatidylinositol 3-kinase-dependent pathway. In addition, \( \alpha \)-adrenergic stimulation promotes translocation of glucose transporter 4 and thus glucose transport (13). These effects are in addition to \( \beta \)-adrenergic stimulation of insulin release and the subsequent increase in myocardial glucose uptake due to increased plasma insulin levels (18). In the present study, the observed increase in MGU in the younger control group supports the premise that a direct effect on myocardial glucose uptake by dobutamine occurs in humans (see Table 4).

Effect of Aging on Myocardial Metabolic Response to Catecholamines

In contrast with younger individuals, older individuals experienced an increase in MFAU and MFAO but not MGU in response to dobutamine administration (see Tables 3 and 4). The blunted MGU response cannot be explained by differences in the responses to dobutamine infusion in plasma substrates or insulin (see Table 1), hemodynamics, MBF or MV\(_2\) (see Table 2). However, aging is associated with an increase in resting catecholamine levels, a resultant downregulation of the \( \beta \)-adrenergic receptors, and thus an impaired myocardial response to exercise and to catecholamines (25). The impairment in MGU and lack of impairment in MFAU and MFAO may be related to the differential \( \beta \)-adrenergic receptor response to aging. Both \( \beta_1 \) and \( \beta_2 \)-receptor sensitivity decrease with age, but \( \beta_2 \)-receptor sensitivity does not decline (24, 27, 36). The \( \beta_1 \) and \( \beta_2 \)-receptors play a key role in myocardial glucose uptake, and a decline in sensitivity with age would result in a reduction in MGU (11, 17). In contrast, MFAU and MFAO are driven to a large extent by plasma fatty acid levels. Plasma fatty acid levels in turn are determined by the degree of lipolysis in peripheral adipocytes, a process that is modulated by \( \beta_3 \)-receptors in adipose tissue (27). Thus the response of MFAU and MFAO to dobutamine infusion may be less affected by age. The similar increases in plasma FFAs and MFAU and MFAO in the younger and older volunteers in response to dobutamine infusion (see Table 1) support this contention.

Study Limitations

Lactate is another significant source of energy for the heart at rest and during exercise (16), and lactate metabolism was not measured in the present study. As mentioned previously, lactate uptake can increase significantly with catecholamines and typically parallels the increase in myocardial workload (20). In the present investigation, although plasma lactate levels were higher at rest in older individuals, lactate levels did not increase in either group with dobutamine infusion (see Table 1). Moreover, increases in plasma fatty acids should suppress myocardial lactate uptake (16). This observation makes it less likely that a relative...
increase in lactate utilization in the older hearts compared with the younger hearts compensated for the lack of augmented MGU during dobutamine infusion in the present study.

The present study of a dobutamine-induced increase in cardiac work is not representative of exercise-induced changes in myocardial metabolism. In the former, there is no increase in skeletal muscle production of lactate to raise serum lactate levels, whereas β-adrenergic-induced lipolysis raises FFA levels. During exercise, however, lactate uptake and oxidation increase significantly due to the high concentrations that result from skeletal muscle lactate production. In contrast, β-adrenergic FFA release is balanced by skeletal muscle FFA consumption and results in only an upward trend in FFA level with exercise. Increases in myocardial lactate uptake correlate with increases in plasma lactate levels (16). In the present study, no changes in lactate levels were observed between individuals at rest and with dobutamine infusion; thus it is unlikely that changes in lactate levels resulted in the observed age-related differences in glucose utilization.

The compartmental model used in this study only permits the measurement of overall MGU and does not estimate the fraction of extracted glucose that is either stored as glycogen or is further metabolized via oxidative and nonoxidative pathways. It is likely that the fraction of extracted glucose that is metabolized to lactate or CO₂ is increased during dobutamine infusion (17). However, to our knowledge, there are no data to support the idea that the increase in glucose metabolism with catecholamines becomes more pronounced with age. The present study does not take into account the dependence of the myocardium on endogenous sources for substrates such as glycogen and triglycerides. As mentioned previously, in the isolated working rat heart, the contribution of glycogen as a source of substrate is most prominent during the first 10 min after epinephrine stimulation. However, this effect was transient and observed in a milieu of constant substrate levels (17). Our data collection began at least 120 min after the initiation of dobutamine infusion; thus it is unlikely that glycogenolysis contributed significantly to the MGU measured in the present study. Under conditions of adequate plasma fatty acid levels, the contribution of ATP from oxidation of fatty acids from exogenous fatty acids is four to eight times greater than that produced from oxidation of endogenously produced fatty acids (31). To our knowledge, there are no data to support the notion that oxidation of endogenously produced fatty acids in response to catecholamine stimulation increases with age.

Finally, differences in cardiac work may have partially accounted for the age-related differences in myocardial metabolic response to dobutamine infusion. It is well established that both cardiac chronotropic and contractile responses to catecholamines diminish with age (25). Thus the metabolic response observed in the older group may have reflected a lower cardiac work level during dobutamine infusion. The lack of differences between the groups in MVO₂ and RPP in response to dobutamine infusion in the present study (see Table 2) is likely due to the relative insensitivity of the RPP to changes in cardiac work.

Clinical Implications

The clinical ramifications of the observed age-related differences in the myocardial metabolic response to catecholamines remain to be determined. One could posit that the lack of increase in MGU in response to dobutamine infusion leads to a state of energy deprivation, and this could partially explain the age-related decrease in contractile function during stress. Moreover, if the aged heart during stress is more dependent on fatty acids as a source of energy, then it may be more susceptible to manifestations of myocardial ischemia due to inhibition of β-oxidation. Additional studies will be necessary to clarify these issues.

DISCLOSURES

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