Clinical Course of Mesenteric Artery Stenosis in Elderly Americans

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Background: To examine prospectively the relationship between stenosis or occlusion of the celiac and superior mesenteric arteries and symptoms of chronic intestinal ischemia in free-living elderly patients in the United States.

Methods: As part of an ancillary study to the Cardiovascular Health Study, participants in the Forsyth County (North Carolina) cohort underwent visceral duplex ultrasonography of the celiac and superior mesenteric arteries. Critical mesenteric artery stenosis (MAS) or occlusion was defined by Doppler flow ultrasound–derived criteria. Clinical outcomes were assessed at annual follow-up examinations and review of death certificates. Multivariate associations between the presence of MAS and all-cause mortality and adverse cardiovascular events were analyzed. Participants with MAS were contacted to determine the presence of symptoms consistent with chronic intestinal ischemia.

Results: Of 553 participants who underwent visceral duplex ultrasonography, 97 (17.5%) had disease of the celiac or superior mesenteric artery. At a mean follow-up of 6.5 years, 20 participants with MAS (20.6%) and 93 without MAS (20.4%) had died (relative risk, 1.01; 95% confidence interval, 0.66-1.55). No deaths were attributed to intestinal infarction. No association existed between the presence of MAS and prevalent cardiovascular disease, all-cause mortality, or adverse cardiovascular events. A questionnaire was completed by 71% of the surviving participants with MAS. No participant reported symptoms or weight loss consistent with chronic intestinal ischemia.

Conclusions: Mesenteric artery stenosis was a common finding in free-living elderly patients. At long-term follow-up, the presence of asymptomatic MAS was not associated with death or adverse cardiovascular events. Participants with asymptomatic MAS by duplex ultrasonographic criteria did not experience intestinal infarction or develop chronic intestinal ischemia.

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Wide spread application of sophisticated medical imaging techniques will define asymptomatic vascular disease in our aging population. Technical improvements in duplex ultrasonography (US), magnetic resonance angiography, and computed tomographic angiography enable high-resolution, noninvasive vascular imaging. Whole-body noninvasive imaging is marketed directly to the public despite a lack of level I evidence to support this practice. Often, vascular lesions are identified during evaluation of an unrelated clinical disorder. A physician may, thus, find asymptomatic mesenteric arterial stenosis or occlusion. Compared with carotid, coronary, renal, and peripheral vascular disease, few natural history data exist for the clinical course of asymptomatic disease involving the major mesenteric arteries. Autopsy-based estimates of prevalent mesenteric disease range from 30% to 80%. Angiographic case series have defined associations between symptomatic peripheral atherosclerosis and renal atherosclerosis with unsuspected mesenteric arterial lesions; however, population-based data are lacking.

A recent population-based study identified asymptomatic celiac axis (CA) or superior mesenteric artery (SMA) stenosis at duplex US in 17.5% of an elderly, free-living cohort. Most of these participants had isolated CA stenosis. Superior mesenteric artery disease was present in only 2.5% of the population but was associated with renal artery stenosis and weight loss. Lesions of the SMA were uncommon in the cohort, yet the association with weight loss suggested that SMA stenosis may have important clinical significance.
Blood pressure and weight measurements were obtained at each annual follow-up visit. Repeated blood studies were performed at the 1992-1993 and 1996-1997 follow-up visits and at visceral duplex US (VDUS).

VISERIAL DUPLEX ULTRASONOGRAPHY

As an ancillary study funded through the National Institute of Diabetes and Digestive and Kidney Diseases, CHS participants in the Forsyth County (North Carolina) cohort underwent abdominal duplex US between January 18, 1995, and January 31, 1997. The primary purpose of this ancillary study was to define the prevalence of renovascular disease in the Forsyth County cohort. An additional goal was to determine the presence or absence of mesenteric artery disease, defined as celiac axis and SMA stenosis or occlusion. All Forsyth County CHS participants scheduled for routine annual examination during the ancillary study period were contacted by telephone and invited to participate in the study. This study was approved by the Wake Forest University Human Subjects Review Committee.

Visceral duplex US was performed with a 96-channel phased, linear and curved linear, high-definition array ultrasound system (Ultramark-9 HDI; Advanced Technologies Laboratories, Bothell, Wash). All VDUS was performed by 2 registered vascular technologists with extensive experience in abdominal duplex US evaluation. Written informed consent was obtained from CHS participants when they returned for their annual examination. During that same visit, consenting participants underwent VDUS at the CHS Forsyth County Field Center, Winston-Salem, NC. As part of the annual examination, CHS participants had fasted overnight.

A complete duplex US examination was performed to examine both renal arteries, the celiac axis, and the SMA. Renal duplex US (RDUUS) was performed first, followed by VDUS. To minimize participant burden, the protocol design allowed 20 minutes in which to complete the entire examination. With the participant in the supine position, a 2.25- or 3.0-MHz ultrasound probe was coupled to the abdominal skin with acoustic gel 3 to 4 cm inferior to the xiphoid process. Intergrogation of each renal artery, the celiac axis, and the SMA was performed as described.9,10

All B-mode and Doppler spectral data were collected on super-VHS (video home system) tape and transferred to an electronic database. This process was repeated, and the data were compared for agreement. A 3% discordance in electronic data was adjudicated from review of the original duplex US study. Results of VDUS were considered negative or positive for hemodynamically significant mesenteric artery stenosis (MAS), defined as CA peak systolic velocity greater than 200 cm/s or SMA peak systolic velocity greater than 270 cm/s. These VDUS criteria for diameter-reducing arterial stenosis of 70% or greater have been examined retrospectively and validated prospectively in comparison with conventional mesenteric angiography.10,11

PATIENT FOLLOW-UP

Data obtained from VDUS examinations were integrated with surveillance CHS data for incident cardiovascular events (myocardial infarction; angina, congestive heart failure, or claudication requiring hospitalization; stroke or transient ischemic attack, and coronary intervention) and all-cause mortality. The dates of all cardiovascular events were recorded, and cause of death was recorded for all participants who died. Surviving participants found to have celiac axis or SMA stenosis and occlusion were contacted by telephone. A 7-item questionnaire was administered by 1 of us (D.B.W.) to enable standardized assessment of a participant’s gastrointestinal tract as well as a specific query related to symptoms consistent with intestinal ischemia (Figure).

STATISTICAL ANALYSIS

After ancillary study data were keyed and verified, results of duplex US examinations were matched with participant data.
provided by the CHS Coordinating Center. Univariate comparison of demographic and atherosclerotic risk factors among participants who underwent duplex US, with and without completed mesenteric questionnaires, was performed using t tests and χ² tests, or the Fisher exact test if warranted by small expected cell counts. Similar analyses were performed to examine demographic data and cardiovascular disease risk factors between participants with and without mesenteric ischemia at RDUS as defined in Table 1. Two follow-up outcomes were examined: all-cause mortality and fatal or nonfatal adverse cardiovascular events (occurrence of fatal cardiovascular disease; myocardial infarction; angina, congestive heart failure, or claudication requiring hospitalization; stroke or transient ischemia attack; or coronary procedure). Univariate description of follow-up outcomes by MAS status was performed by estimating relative risk using 2-way contingency tables. Examination of potential multivariable relationships between MAS and follow-up outcomes was performed using proportional hazards regression models. Final regression models were constructed for each outcome using a forward stepwise variable selection procedure. Covariates significant to the .10 level were introduced, beginning with the most significant, and remained if significant at the .05 level. Covariates considered in multivariable models included the following: age, race, and sex; weight at RDUS examination; smoking history; systolic and diastolic blood pressure; hypertension status; antihypertensive medication use; serum creatinine concentration; statin drug use; diabetes; and history of a coronary procedure, angina, myocardial infarction, atrial fibrillation or pacemaker, congestive heart failure, stroke or transient ischemic attack, carotid endarterectomy, peripheral vascular disease, major electrocardiographic abnormalities, or left ventricular function abnormalities at electrocardiography or echocardiography.

**RESULTS**

Of 1145 participants eligible for inclusion, 870 (76%) agreed to participate in the ancillary study. Of 870 studies attempted, 553 (64%) were technically adequate to determine visceral disease status. Comparison of participant demographic data and atherosclerotic risk factors among participants who underwent duplex US, with and without complete mesenteric examinations, is given in Table 1. Of participants with complete mesenteric examinations, fewer were men (31% vs 49%), they had a lower prevalence of smoking (current or former smokers, 44% vs 51%), they weighed less (mean±SD, 157±30 lb vs 168±33 lb [71±14 kg vs 76±15 kg]), and they had higher mean levels of total cholesterol (211±37 mg/dL vs 205±37 mg/dL [5.56±0.96 mmol/L vs 5.30±0.96 mmol/L]) and high-density lipoprotein cholesterol (55±16 mg/dL vs 52±14 mg/dL [1.42±0.41 mmol/L vs 1.34±0.36 mmol/L]).

Overall, 97 (17.5%) of 553 participants with technically adequate VDUS examinations had MAS. Of the 97 participants with MAS, 83 (86%) had isolated CA stenosis, 7 (7%) had combined CA and SMA stenosis, 5 (5%) had isolated SMA stenosis, and 2 (2%) had CA occlusion. The prevalence of these anatomical subgroups of MAS in the entire study cohort was 15.0%, 1.3%, 0.9%, and 0.4%, respectively.

Table 2 summarizes characteristics and cardiovascular disease risk factors in participants with complete mesenteric duplex US examinations. Results are categorized by “SMA/cecal occlusion,” “celiac stenosis,” and those with “normal” examination results. Univariate comparison of factors among participants with SMA or CA occlusion vs those with normal results demonstrated significant differences only in prevalence of lipid-lowering medication use (29% vs 9%, respectively; P=.03). Comparison of factors among participants with CA stenosis vs those with normal results demonstrated that the former group had a higher prevalence of hypertension (61% vs 49%, respectively; P=.04), higher mean systolic blood pressure (mean±SD, 144±22 mm Hg vs 135±20 mm Hg [65, respectively; P<.001], and lower mean weight (mean±SD, 149±28 lb vs 158±31 lb [67±13 kg vs 71±14 kg]; P=.008).

At a mean follow-up of 6½ years, there was no statistically significant association between the presence of MAS and either all-cause mortality or incident cardiovascular events (Table 3). Analysis of the subgroup of participants with either isolated SMA stenosis, combined SMA and CA stenosis, or CA occlusion was performed. No association between the presence of this pattern of disease and either all-cause mortality or adverse cardiovascular events was demonstrated (Table 3). Addition of covariates to multivariable models including MAS status did not affect that factor’s association with outcomes. Of 97 participants with MAS, 63 were presumed alive based on CHS clinic records, and 45 (71%) of these were...
available to complete the 7-item questionnaire at the time of this analysis. At mean follow-up of 6.8 years, none of these participants reported postprandial pain, change in diet to avert pain, substantial unintended weight loss, interval endoscopic or radiographic gastrointestinal tract imaging, or a diagnosis of mesenteric ischemia. Of 10 participants who had undergone cholecystectomy, all had symptomatic relief after the procedure.

**COMMENT**

To our knowledge, the present study is the first to combine long-term prospective clinical follow-up and cross-sectional anatomical data about mesenteric artery disease in a population-based cohort. The presence of hemodynamically significant MAS was not associated with subsequent acute or chronic intestinal ischemia, gastrointestinal tract interventions, excessive cardiovascular events, or increased mortality. These data suggest that asymptomatic stenoses and occlusions of the CA or SMA in elderly patients demonstrate an uneventful natural history.

The lack of association between mesenteric artery disease and adverse cardiovascular outcomes differs from participants in this cohort with renal artery stenoses. This result may reflect sequelae associated with activation of the renin-angiotensin system in renovascular disease. Alternatively, it might be explained by a nonatherosclerotic source of MAS in this cohort. Extrinsic compression of the CA by the median arcuate ligament is well described, but its clinical relevance is debated.
US in this study. Thus, a subgroup analysis of those participants least likely to have extrinsic compression was performed. Data for participants with isolated SMA stenosis, combined CA and SMA stenosis, or total CA occlusion were analyzed separately. Fourteen of 97 participants with any MAS had such lesions. Although no association between the presence of this pattern of disease and adverse cardiovascular outcomes or subsequent onset of symptoms was demonstrated, the few participants identified with MAS, and, in particular, with SMA or CA occlusion, would require any underlying associations with events to be extremely large to be observed.

Of the 45 patients who had MAS and were available for follow-up, 10 (22%) had a history of cholecystectomy. Although the exact prevalence of cholecystectomy in the United States is unknown, the 22% in our cohort is in keeping with that reported in other large studies. Since these patients all experienced resolution of symptoms after cholecystectomy, it is reasonable to assume that the symptoms were not associated with MAS.

Previous investigators have documented a low rate of progression from asymptomatic to symptomatic mesenteric disease among selected patients. Thomas et al observed a cohort of patients with known atherosclerosis and an indication for aortography who were found to have asymptomatic stenosis greater than 50% of the CA, SMA, or inferior mesenteric artery. Of 980 consecutive biplane aortograms, obtained primarily in patients with peripheral vascular disease, 82 patients had significant mesenteric disease, and 72 of these were observed prospectively. Sixty patients with high-grade stenosis of 1 or more vessels were examined. Four patients developed subsequent symptoms of chronic intestinal ischemia during a mean follow-up of 30 months. All had severe stenosis or occlusion of all 3 mesenteric arteries. One patient died from acute mesenteric ischemia associated with extensive bowel gangrene.

Asymptomatic disease of the mesenteric arteries will be identified more frequently in the future. High-resolution computed tomographic angiography, magnetic resonance angiography, and duplex US are widely available and are used in evaluation of a variety of abdominal diseases. Collectively, they are the primary methods by which incidental MAS is identified. A potential value of this article is that the study cohort may reflect the population at large subjected to abdominal imaging. Our findings suggest that conservative management of asymptomatic mesenteric stenosis is safe and that intervention to treat asymptomatic MAS is unwarranted.

Several limitations of this study deserve comment. Indexed subjects from the CHS were collected through a 2-step random process; however, eligible members from the sampled individual’s household were also recruited. This strategy was intended to enhance recruitment and retention of the elderly cohort for longitudinal observation. As a result, the final CHS cohort consisted of 70% of those initially sampled and 30% who were recruited because they shared the same household. This recruitment strategy may have introduced an important source of bias, since significant differences existed between randomly selected participants and those who chose not to participate in the CHS. The refusal rate was higher among women than men, and enrolled participants were younger, more highly educated, more likely to be married, and less likely to be smokers. In addition to this healthy-cohort effect, the recruitment for VDUS may have introduced other sources of bias. Compared with the 870 CHS participants recruited for duplex US study, the 375 participants who declined study were older, had a greater history of tobacco use, and had a significantly lower proportion of obesity. Each of these characteristics may have contributed to underestimation of the incidence of MAS.

The protocol for VDUS may have introduced unintended bias. Visceral duplex US was performed in this cohort as part of an ancillary study that included RDUS. The specific purpose of the RDUS examination was to determine the presence or absence of hemodynamically significant renal artery stenosis or occlusion; the evaluation for MAS or mesenteric artery occlusion was a secondary goal. To minimize the study burden on this elderly cohort, the duplex US protocol limited the entire examination to 20 minutes. Ninety-six percent of the

### Table 3. Associations Between Mesenteric Artery Disease and Follow-up Events

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome, %</th>
<th>Mesenteric Artery Disease, No. (%)</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any mesenteric stenosis†</td>
<td>All-cause mortality‡</td>
<td>24/97 (24.7)</td>
<td>0.9 (0.6-1.5)</td>
<td>.76</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular event§</td>
<td>27/97 (27.8)</td>
<td>0.9 (0.6-1.3)</td>
<td>.45</td>
</tr>
<tr>
<td>SMA stenosis or occlusion, or CA occlusion</td>
<td>All-cause mortality§§</td>
<td>3/14 (21.4)</td>
<td>0.5 (0.1-2.9)</td>
<td>.37</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular event§§</td>
<td>2/14 (13.3)</td>
<td>0.4 (0.1-1.6)</td>
<td>.39</td>
</tr>
</tbody>
</table>

Abbreviations: CA, celiac axis; CHF, congestive heart failure; CI, confidence interval; PSV, peak systolic velocity; RDUS, renal duplex ultrasonography; SMA, superior mesenteric artery; TIA, transient ischemic attack.

†Derived from multivariate proportional hazards regression models.
‡Defined as all-cause mortality adjusted for the following factors selected via forward stepwise model building: history of diabetes, CHF, stroke or TIA, or abdominal aneurysm or repair; left ventricular function abnormality at echocardiography; serum creatinine concentration; age at RDUS examination; and weight at RDUS examination.
§Defined as myocardial infarction, angina, CHF, or peripheral vascular disease hospitalization, coronary revascularization, stroke, or TIA. Models for cardiovascular event adjusted for the following factors selected via forward stepwise model building: history of diabetes, claudication or lower extremity vascular procedure, angina, or abdominal aneurysm or repair; use of hypertensive medications; serum creatinine concentration; and age at RDUS examination.
RDUS examinations were technically satisfactory; however, study time was inadequate for simultaneous VDUS in one third of participants.\(^\text{18}\) Compared with participants with adequate VDUS examinations, participants with inadequate studies were more likely to be men, had a greater history of tobacco use, and had higher mean total and lower high-density lipoprotein cholesterol levels (Table 1). These are well-established risk factors for atherosclerosis and may have resulted in decreased prevalence of MAS in this study population.

Another limitation of this study was the advanced age of the cohort. At the time of survey, the participants’ ages ranged from 77 to 98 years (mean and median ages, 84 years). Seventeen participants died in the year since the CHS data were last updated; the cause of death in these participants was unavailable. Of the survivors, 30% had either relocated without providing contact information or refused the survey. Consequently, we may have underestimated the incidence of adverse cardiovascular events or symptoms of intestinal ischemia.

Despite these potential limitations, to our knowledge, this study provides the first prospective population-based study of asymptomatic MAS. The presence of stenosis was not associated with subsequent acute or chronic mesenteric ischemia. These data suggest that asymptomatic disease of the celiac axis or SMA may be safely observed and that prophylactic intervention is not warranted.

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