Association Between Thoracic Aortic Disease and Inguinal Hernia

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Background—The study hypothesis was that thoracic aortic disease (TAD) is associated with a higher-than-expected prevalence of inguinal hernia. Such an association has been reported for abdominal aortic aneurysm (AAA) and hernia. Unlike AAA, TAD is not necessarily detectable with clinical examination or ultrasound, and there are no population-based screening programs for TAD. Therefore, conditions associated with TAD, such as inguinal hernia, are of particular clinical relevance.

Methods and Results—The prevalence of inguinal hernia in subjects with TAD was determined from nation-wide register data and compared to a non-TAD group (patients with isolated aortic stenosis). Groups were balanced using propensity score matching. Multivariable statistical analysis (logistic regression) was performed to identify variables independently associated with hernia. Hernia prevalence was 110 of 750 (15%) in subjects with TAD versus 29 of 301 (9.6%) in non-TAD, $P=0.03$. This statistically significant difference remained after propensity score matching: 21 of 159 (13%) in TAD versus 14 of 159 (8.9%) in non-TAD, $P<0.001$. Variables independently associated with hernia in multivariable analysis were male sex (odds ratio [OR] with 95% confidence interval [95% CI]) 3.4 (2.1 to 5.4), $P<0.001$; increased age, OR 1.02/year (1.004 to 1.04), $P=0.014$; and TAD, OR 1.8 (1.1 to 2.8), $P=0.015$.

Conclusions—The prevalence of inguinal hernia (15%) in TAD is higher than expected in a general population and higher in TAD, compared to non-TAD. TAD is independently associated with hernia in multivariable analysis. Presence or history of hernia may be of importance in detecting TAD, and the association warrants further study. (***J Am Heart Assoc***. 2014;3:e001040 doi: 10.1161/JAHA.114.001040)

Key Words: aneurysm • aorta • risk factors • surgery

An association between abdominal aortic aneurysm (AAA) and abdominal wall hernia—primarily inguinal hernia—has been found in several studies.[1–4] Dysequilibrium in connective tissue homeostasis, including collagen type I/type III ratio[5,6] and matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs),[7,8] has been suggested as common features of AAA and hernia. A similar association between hernia and thoracic aortic disease (TAD), that is, predominantly thoracic aortic aneurysm (including thoracoabdominal aneurysm) and aortic dissection, is plausible. The risk factors for TAD differ from those of AAA. Apart from hypertension (HTN), the etiology of TAD is seldom arteriosclerosis,[9] but more often related to congenital conditions (specifically,

bicuspid aortic valve [BAV] and aortic coarctation), genetic mutations, or family history.[10–12] Consequently, an association between different expressions of connective tissue dysregulation could be even more pronounced in TAD than AAA. We hypothesized that the prevalence of inguinal hernia is increased and higher than expected in subjects with TAD. The specific study aims were to determine the prevalence of hernia in a TAD population, characterize the hernia prevalence in TAD subgroups, and elucidate the association between TAD and hernia by comparison to a non-TAD group.

Methods

All subjects presently or previously attending regular follow-up at a referral aortic outpatient clinic were eligible for inclusion in a cross-sectional follow-up study. Subjects with other forms of TAD than dissection or aneurysm were excluded, as were subjects attending controls because of increased risk, but themselves determined free of TAD by imaging studies. The resulting study group included 750 subjects, 654 (87%) alive at the time of cross-sectional follow-up. For comparison, a group of 301 patients operated on for isolated aortic stenosis (AS), that is, without significant aortic regurgitation, annulo-aortic ectasia, or ascending aortic dilatation, devoid of other

structural heart disease and significant coronary artery disease, was identified. The rationale for using a cohort of patients operated on for pure AS as a comparison group was based on (1) certainty of freedom from TAD, based on preoperative examinations, (2) patients recruited from the same population, that is, from the same geographical area and during a similar time span, (3) patient data were prospectively collected and included presence of BAV, otherwise impossible to obtain, and (4) the majority were elderly males, implicating a higher hernia prevalence than a healthy normal population and thus yielding conservative findings. The study was approved by the regional research ethics committee. Written informed consent was obtained from all live participants.

Data Sources and Data Management

Separate local research databases covering TAD and non-TAD groups, respectively, consisted of prospectively collected demographic and clinical (including imaging and surgical) data and were >95% complete for each of the included variables, except for height and weight (81% and 86% completeness, respectively). Consequently, with missing data, body mass index (BMI) was imputed as conditional (group, gender) mean. For categorical variables, single missing data were defaulted to "absent," yielding conservative estimates. Data on hernia were accrued from a single source for both cases and controls, namely, the national patient register provided by the Swedish National Board of Health and Welfare. The register includes inpatient, outpatient, and surgical day care episodes from 1987 to 2011. The register was queried for applicable diagnostic (International Classifications of Diseases [ICD], ninth [ICD-9] and tenth revision [ICD-10]) and procedural codes for abdominal wall hernia and surgical hernia repair (Table 1). The national Swedish inpatient register has been

Table 1. Diagnostic and Procedural Codes Used to Identify Hernia and Surgical Hernia Repair in National Patient Registers

Diagnosis	ICD-10	ICD-9
Hernia	K40 to K43	550 to 553
Surgical procedure	NOMESCO	NBHW
Surgical hernia repair	JAB to JAF	4200 to 4206
		4210 to 4213
		4240 to 4244
		4260 to 4263

Diagnostic codes: International Classification of Diseases (ICD), tenth (ICD-10) and ninth (ICD-9) revisions. Procedural codes: Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (in use since 1997) and National Board of Health and Welfare (NBHW) Classification of Operations, 6th revision.

validated repeatedly. Specifically, for hernia and hernia repair, the register was 92.5% complete with a positive predictive value of 0.94 and a negative predictive value of 1.0.[13]

Definitions

Hernia was classified as unilateral inguinal, bilateral inguinal, or other abdominal wall hernia. No distinction was made between direct and indirect inguinal hernia. Surgical repair was classified as single or multiple, based on number of unique registrations. Aortic dissection was subdivided by the Stanford classification (type A and type B, respectively), whereas thoracic aortic aneurysm was subdivided according to involved aortic segment(s): ascending aorta, aortic arch, descending and thoracoabdominal aorta, respectively, with possibility of several involved segments in a single individual. Definitions of other conditions included HT: blood pressure >140/90 mm Hg or requiring at least 1 medication to obtain normotension. Diabetes and chronic obstructive pulmonary disease (COPD), respectively: requiring pharmacological therapy. Smoking: earlier or ongoing habitual smoking, that is, distinguishing between ever- and never-smokers. Obesity: BMI >30 kg/m^2. History of cerebrovascular incident: stroke or transient ischemic attack. BAV, aortic regurgitation, and aortic stenosis were defined from echocardiographic and/or intraoperative findings. Marfan syndrome was defined as clinically and/or genetically established diagnosis.

Statistical Methods

Data are reported as means with SD or as numbers with percentages if not stated otherwise. Means were group-wise compared using Student t test. Proportions were group-wise compared using chi-square (χ^2) tests or Fisher's exact test, as applicable. Multivariable analysis of predictors for hernia was performed with logistic regression. Final model selection was based on maximum likelihood tests in conjunction with the c-statistic and Hosmer-Lemeshow goodness-of-fit test. Results of logistic regression are given as odds ratios (ORs) with 95% confidence interval (CI). OR and 95% CI were estimated with a bootstrapping procedure (1000 repetitions, with replacement). The prevalence of hernia in TAD subjects was compared to non-TAD subjects. Using logistic regression including all available covariates (nonparsimonious model), a propensity score was generated for each patient, corresponding to the probability of having TAD. Subjects from the TAD group and non-TAD group were matched using the propensity score. Nearest neighbor 1:1 matching without replacement was applied, with a caliper of $0.2 \times SD$ of the propensity score logit, as proposed by Austin.[14] The effectiveness of balancing with the propensity score is reported in terms of standardized differences and bias reduction (Table 2). Acknowledging the

Table 2. Clinical Characteristics of the Study Group (TAD) and Comparison Group (Non-TAD) Before and After Propensity Score Matching

Characteristic	Before Matching			After Matching			
	TAD (n=750)	Non-TAD (n=301)	% Stand Diff	TAD (n=159)	Non-TAD (n=159)	% Stand Diff	% Bias Red
Age, y	61±13	69±10	−66	69±11	69±11	0.4	99
Male sex	506 (67)	179 (59)	17	98 (62)	100 (63)	2.6	84
BMI, kg/m^2	26±3.9	27±4.6	−33	27±4.1	27±4.5	2.8	91
Obesity	17 (2.3)	78 (26)	−72	5 (3.1)	37 (23)	62	15
Smoking	279 (37)	181 (60)	−47	88 (55)	84 (53)	5.2	89
COPD	48 (6.4)	11 (3.6)	13	9 (5.7)	9 (5.7)	0	100
Hypertension	563 (75)	218 (72)	6.0	118 (74)	120 (75)	−2.9	56
CVI	92 (12)	33 (11)	4.1	23 (14)	24 (15)	−2.0	53
Diabetes	21 (2.8)	42 (14)	−41	9 (5.7)	12 (7.5)	−7.0	83
BAV	71 (9.5)	157 (52)	−104	46 (29)	48 (30)	−3.1	97
AS	51 (6.8)	301 (100)	−523	21 (13)	159 (100)	−487	6.9
Marfan	25 (3.3)	0	26	2 (1.2)	0	9.9	62
AAA	n/a	3 (1.0)	n/a	0	0	0	100

Mean±SD and count (percentage), respectively. AAA indicates abdominal aortic aneurysm; AS, aortic stenosis; BAV, bicuspid aortic valve; Bias Red, bias reduction (achieved by propensity score matching); BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVI, cerebrovascular insult; n/a, not applicable; Stand Diff, standardized difference; TAD, thoracic aortic disease.

resulting individually matched-pair construction, McNemar's test was used in comparison of hernia prevalence.[15] Statistical analysis was carried out using Stata (v12.1; StataCorp LP, College Station, TX).

Results

Hernia was found in 110 of 750 (15%) of subjects with TAD, versus 29 of 301 (9.6%) in the non-TAD group, *P*=0.030. Of these, 58 (53%) had been operated on for their hernia, and in 9 (8.2%), bilateral inguinal hernia were present. Only 3 (0.4%) had a noninguinal abdominal wall hernia. Three subjects with Marfan syndrome had hernia, for a prevalence of 12% (3 of 25). In the TAD group, hernia was reported in 7 of 71 (9.9%) with BAV, compared to 103 of 679 (15%) with tricuspid aortic valve, *P*=0.23. Hernia was equally common in patients that had been operated on for TAD versus nonoperated: 54 of 373 (14%) versus 56 of 377 (15%), *P*=0.88. The distribution of hernia in aneurysm versus dissection is illustrated in the Figure. There were no statistically significant differences between hernia prevalence in aneurysm versus dissection or proximal versus distal aorta. Characteristics of TAD and non-TAD groups are presented in Table 2. In univariate analysis, TAD (*P*=0.031), male sex (*P*<0.001), COPD (*P*=0.041), and diabetes (*P*=0.028) were related to hernia. Marfan syndrome, BAV, smoking, and type of TAD (aneurysm vs. dissection, location of aneurysm, and Stanford type dissection) were not

significantly related to hernia. In multivariable analysis using logistic regression, age, male sex, and TAD were independently related to hernia (Table 3).

Propensity score matching yielded 159 matched pairs. For all variables except obesity, propensity score matching yielded a reduction in standardized difference to <10%. By
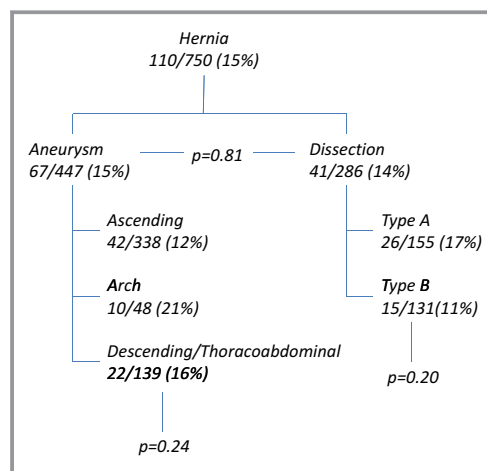

Figure. Distribution of inguinal hernia in subjects with thoracic aortic disease. Subjects with thoracic aortic aneurysm subdivided by anatomical location. Subjects with aortic dissection subdivided by Stanford type (A—including ascending aorta; B—distal to ascending aorta).

Table 3. Multivariable (Logistic Regression) Statistical Analysis of Independent Predictors of Hernia

Variable	OR	95% CI	P Value
Male sex	3.4	2.1 to 5.4	<0.001
Thoracic aortic disease	1.8	1.1 to 2.8	0.015
Age (1 year increment)	1.02	1.004 to 1.04	0.014

Likelihood ratio χ^2=38; c-statistic=0.66; goodness-of-fit P=0.53. CI indicates confidence interval; OR, odds ratio.

default, the differences in the group-defining conditions (TAD and non-TAD, respectively) remained. Among the propensity score-matched pairs, hernia was significantly more prevalent in the TAD group versus non-TAD group: 21 of 159 (13%) versus 14 of 159 (8.8%); OR, 9.9 (95% CI, 5.7 to 18); P<0.001.

Discussion

Supporting the hypothesis of the present study, the prevalence of inguinal hernia in adult individuals with known TAD appears to be pronouncedly increased; 15% in a cohort of 750 individuals with different expressions of TAD. The prevalence was significantly higher than the 9.6% found in a non-TAD comparison group (operated on for isolated AS) from the same population. The prevalence of hernia was evenly distributed between aneurysm and dissection and anatomic locations of TAD (Figure). In multivariable statistical analysis, TAD was independently associated with hernia (Table 3), together with the universally appearing hernia risk factors of male sex and increased age.[16] No other studied variables, including BMI, smoking, COPD, and different expressions of connective tissue disorders (Marfan syndrome and BAV), were independently related to hernia. The finding was confirmed after propensity score matching and comparison of the resulting 159 matched pairs.

Hernia Prevalence in TAD Versus General Population

In population studies, the true prevalence of hernia is difficult to estimate and depends on a multitude of factors, including, but not restricted to, diagnostic criteria, study methodology, ethnical and regional differences, and surgical activity. In the 1960 U.S. health survey, 15 of 1000 (1.5%) of responders had a groin hernia,[17] whereas in the comprehensive 4th Morbidity Survey in General Practice in the UK (1990), the estimated prevalence of inguinal and femoral hernia combined was 247 in 100 000 (0.25%).[18] Elective hernia repair is often performed in an outpatient setting and with extremely low mortality rate (≈5 in 100 000), in contrast to complicated

hernia repair (strangulation, incarceration) with a 10-fold mortality rate.[19] Therefore, the "demand" incidence, based on surgical procedures, is a reasonable approximation of clinically relevant hernia. In Denmark, it was recently reported to be 0.82% (46 717 hernia repairs in a population of 5 639 885 over 5 years) with a peak prevalence of 4.1% in 75- to 80 year-old males.[20] Thus, the confirmed 15% hernia prevalence (observation time, 1987 to 2011) in the present TAD cohort seems to reflect a substantial over-representation in this group.

AAA and Hernia

In contrast to TAD, the association between hernia and AAA has been reported on repeatedly. In a population-based study from the Mayo clinic, the prevalence of abdominal wall hernia was 16.7% among 939 AAA subjects,[1] demonstrating a significant relationship. Hall et al., retrospectively comparing the prevalence of hernia in patients operated for AAA (n=128) and aortoiliac occlusive disease (AIOD; n=65), found significantly more incisional (10% vs. 3%; P<0.05) and recurrent (28% vs. 19%; P<0.01) hernias in AAA patients[2]; findings corroborated by Raffetto et al, reported a 9-fold increased risk of postoperative hernia formation in AAA versus AIOD.[3] Pleumeekers et al. studied the prevalence of AAA in 156 men operated on for hernia versus 1771 without hernia screened for AAA and found a significantly higher prevalence in the former group (12.2% vs. 3.7%)[4] and even suggested screening for AAA before hernia repair. In crude percentages, hernia appears as common in TAD as in AAA. In the present study, specific data on AAA were not collected for the TAD group because they already, by definition, had aortic disease. In the control group, only 3 subjects (1.0%) had a known AAA, and none of them had hernia. Based on the findings of the present study, it may be speculated that subjects with AAA and hernia more often have a nonarteriosclerotic aneurysm, that is, have a "risk profile" more similar to subjects with TAD or that they, in fact, more often have simultaneous TAD, as reported in 28% of AAA patients.[21]

Possible Common Pathogenetic Mechanisms of Hernia and TAD

The pathogenesis of AAA, TAD, and hernia may share similar basic mechanisms. Reduced function or increased vulnerability of extracellular matrix, related to a dysequilibrium of degrading and restoring forces result in weakened tissue prone to strain-related secondary changes allowing development of aneurysm, dissection—or hernia. The increased activity of transforming growth factor beta 1 (TGF-β1) is unifying to this concept. It increases matrix degradation, is amplified by MMP-2, and is promoted in terms of

bioavailability by the structural changes in fibrillin-1 found in Marfan syndrome.[11] As shown by Béllon et al., increased levels of both MMP-2[22] and active TGF-β1[7] are found in the transversalis fascia of hernia patients. A recent case report describes inguinal hernia at 3 months of age and ascending aortic repair at 12 months of age in a boy with a novel mothers against decapentaplegic homolog 3 (SMAD3) mutation,[23] and hernia was reported in 43% of 44 subjects with the aneurysms-osteoarthritis syndrome caused by SMAD3 variants.[23] However, hernia was not mentioned as a clinically important marker of TAD, neither by van der Linde et al.[24] nor by an accompanying editorial.[25]

BAV and Hernia

Underlying molecular mechanism of aneurysm formation appears different in subjects with bi- and tricuspid aortic valve, respectively.[26–28] Excluding subjects with BAV and Marfan syndrome, the difference in hernia prevalence between the TAD group and the AS group is slightly more pronounced: 100 of 654 (15%) versus 12 of 144 (8.3%), *P*=0.030. In the TAD group, hernia prevalence was increased by some 150% with tricuspid, compared to bicuspid aortic valve (15% vs. 9.9%), but this difference did not reach statistical significance. Our present findings may be most applicable in TAD with tricuspid aortic valve, which is, by far, the largest group of TAD subjects. Moreover, their TAD is less likely to be identified than in patients with bicuspid aortic valve, who may be screened because of known family history or under echocardiographic surveillance owing to aortic valve pathology.

Consideration of Hernia in TAD Guidelines and Screening

Hernia is not mentioned explicitly as a risk factor for TAD in current guidelines,[29] but in the suggested algorithm for acute aortic dissection (AAD), "connective tissue disease" is included as a risk feature. When validated by the IRAD investigators,[30] this particular predisposing condition was excluded, most likely because it was not included in the original IRAD data.[31] Comparing crude numbers, the prevalence of hernia in the present study makes it a more common feature of subjects with TAD than Marfan syndrome (4.9%), earlier aortic dissection (6.4%), and iatrogenic causes (4.3%) in subjects with AAD.[30] Based on the current findings of a high prevalence of hernia in subjects with TAD, it is reasonable to suggest that hernia should be part of the history taking and physical examination of subjects with suspected TAD, even in the setting of suspected AAD, and that its role as a risk factor should be further evaluated to decide whether hernia qualifies among other risk factors cited by guidelines and other studies. Screening programs for TAD remain scarce, given the

need for radiological studies to image the entire aorta, but also because adequately described high-risk groups are lacking. Factors contributing to defining high-risk groups that could benefit from TAD screening are of continued relevance.[24,25] In the relevant age groups, point-prevalence hernia remains below ≈3%.[20] Similarly, in deciding which subjects, if any, with AAA found on ultrasound screening that should have a supplementary chest computed tomography to detect simultaneous AAA and TAD, factors other than traditional cardiovascular risk factors could be of importance.[21]

Study Limitations

The present study has several limitations. It is an observational study unable, by design, to establish a causal link between hernia and TAD. However, such a relationship was not hypothesized. What remains important is that one condition (hernia) may serve as a surrogate marker of the other (TAD), given the high coincidence. Our study includes some, not all, putatively important confounders. Propensity score matching resulted in a reduced number of observations, despite remaining bias in some variables. On the other hand, the association between TAD and hernia was consequent throughout univariate, multivariable, and propensity score-matched analyses. In epidemiological studies, obesity has been associated with decreased hernia prevalence.[16] After balancing groups using the propensity score, obesity remained unbalanced, with a higher prevalence in the non-TAD group (Table 2). The continuous variable, BMI, was, however, well balanced. Obesity was not significant in either uni- or multivariable analysis before propensity score matching. Therefore, we judge it unlikely to confound the findings in any important way.

Population-based epidemiological studies and case-control studies are warranted to confirm the suggested association between TAD and hernia and determine the magnitude of increased risk for TAD in presence of hernia. The present study population consisted almost exclusively of white Caucasians; therefore, the findings may not be applicable to ethnically different populations.

In summary, the study hypothesis of increased hernia prevalence in subjects with TAD was confirmed: At 15%, it was significantly higher than in the comparison group and that is expected in the general population. If confirmed in further studies, the relationship between hernia and TAD should be included in guidelines and considered an integral part of history taking and clinical examination in subjects with TAD.

Acknowledgments

Disclosures

None.

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