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ORIGINAL ARTICLE

# Delayed adverse vascular events after splenectomy in hereditary spherocytosis

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**Summary.** *Background:* It is probable that the variety and frequency of delayed adverse vascular events after splenectomy are underappreciated. Splenectomy is performed for a wide variety of conditions, and delayed postsplenectomy hazards are not often studied. *Objective:* To estimate the relative risk of adverse vascular events in members of hereditary spherocytosis families who have or have not had a splenectomy. *Methods:* Members of families in which hereditary spherocytosis exists were systematically questioned about adverse vascular events. *Results:* The cumulative incidence of arterial and venous events at age 70 years was greater in persons who had undergone a splenectomy for spherocytosis (arterial, 22% females, 32% males; venous, 20% females, 19% males) than in affected persons who did not undergo splenectomy (arterial, 3% females, 2% males; venous, 6% females, 4% males) or non-affected family members (arterial, 10% females, 17% males; venous, 4% females, 12% males). Affected subjects who undergo splenectomy are at greatly increased risk of arterial events as compared to affected subjects who do not undergo splenectomy [arterial, hazard ratio (HR) 7.2, 95% confidence interval (CI) 2.8–17.2; venous, HR 3.3, 95% CI 1.1–9.8]. *Conclusion:* There is a significant, long-lasting, increased risk of adverse arterial and venous thromboembolic events after splenectomy performed for hereditary spherocytosis. A review of the literature indicates that this is also true when splenectomy is performed for several other indications.

**Keywords**: atherosclerosis, osteonecrosis, priapism, pulmonary hypertension, splenectomy, thromboembolism.

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## Introduction

Persistent thrombocytosis is not unusual after splenectomy, and when performed for correction of hemolytic anemia, splenectomy is often followed by increases in the hematocrit, cholesterol and whole blood viscosity, and a decline in serum bilirubin. The University of Wisconsin hematology group has had a continuing research and clinical interest in hereditary spherocytosis for half a century. The accumulated data provide an opportunity to compare rates of adverse vascular events (arterial and venous) in the three subsets of family members: affected spleen out, affected spleen in, and not affected. A 1997 publication [1] based on this database reported that the rate of arterial events after age 40 years was approximately five times higher in hereditary spherocytosis patients without a spleen than in hereditary spherocytosis patients with a spleen. As family members were questioned informally through the years, the impression was gained that adverse venous events were not uncommon. Therefore, over the past 4 years, we have used a formal printed questionnaire to gather data about the incidence of adverse vascular events in the three subsets of subjects arising *a priori* in families known to have hereditary spherocytosis.

## Materials and methods

The hereditary spherocytosis database at the University of Wisconsin Medical Center (UWMC) contains prospectively collected data on 634 persons from families in which hereditary spherocytosis is present, and for whom we are confident of the diagnostic category (affected or unaffected). These data were collected at UWMC between 1960 and 2007. This report is confined to 574 subjects aged 18 years or older at last contact. Of the 434 subjects known to be alive at last contact, 395 (91%) had been contacted and provided data after 1 July 2005. Of the 409 subjects who had not been censored as of 1 July 2005, we obtained data on 360 (88%). For each subject, available data consist of date of birth, date of last contact and, if applicable, dates of death, splenectomy, arterial event (myocardial infarction, stroke, coronary artery surgery, carotid artery surgery),

and venous event (deep vein thrombosis, thrombophlebitis, pulmonary embolus). As of September, 2007, we had reliable data on arterial events for 524 subjects (91%) and on venous events for 443 subjects (77%). Sixty-four persons had an arterial event; 31 had a venous event.

Estimates of the cumulative incidence of arterial events and venous events were calculated for unaffected subjects, affected subjects who had not undergone splenectomy (affected spleen in), and affected subjects who did undergo splenectomy (affected spleen out), using a competing risks model (a modification of the Kaplan–Meier estimate) to account for censoring due to losses to follow-up and the competing risk of death. The estimate for the affected spleen out group represents the cumulative incidence for subjects undergoing splenectomy prior to age 18 years. Cox proportional hazards regression models were used to assess differences between the three groups of subjects. Splenectomy was incorporated into the Cox models as a time-dependent covariate.

## Results

Characteristics of the sample are given in Table 1. Of the 524 subjects with data on arterial events, 236 (45%) are female. Three hundred and fifty-four (68%) have hereditary spherocytosis. Thirty-five per cent (123) of these subjects underwent splenectomy prior to age 18 years. Another 126 (36%) underwent splenectomy after age 18 years. Of the subjects with data on venous events, 236 (45%) are female. Two hundred and ninety (65%) have hereditary spherocytosis. Forty-one per cent (120) of these subjects underwent splenectomy prior to age 18 years. Another 87 (30%) underwent splenectomy after age 18 years.

The reported incidence of hypertension was 28% in unaffected subjects, 26% in affected subjects who did not undergo splenectomy, and 28% in affected subjects who underwent splenectomy. The incidence of diabetes was 12% in unaffected subjects, 12% in affected subjects who did not undergo splenectomy, and 13% in affected subjects who underwent splenectomy.

**Table 1** Demographic data for study of arterial and venous events

| | Males | Females | Total |
|---|---|---|---|
| Subjects with data on first arterial event | | | |
| Unaffected | 85 | 85 | 170 |
| Affected | 203 | 151 | 354 |
| Spleen out before age 18 years | 68 | 55 | 123 |
| Spleen out after age 18 years | 71 | 55 | 126 |
| Spleen in at last contact | 64 | 41 | 105 |
| Total | 288 | 236 | 524 |
| Subjects with data on first venous event | | | |
| Unaffected | 73 | 80 | 153 |
| Affected | 165 | 125 | 290 |
| Spleen out before age 18 years | 65 | 55 | 120 |
| Spleen out after age 18 years | 46 | 41 | 87 |
| Spleen in at last contact | 54 | 29 | 83 |
| Total | 238 | 205 | 443 |

Estimates of the cumulative incidence of first arterial and venous events are provided in Fig. 1. By age 70 years, the cumulative incidence of first arterial events in affected subjects who underwent splenectomy prior to age 18 years was 32% [95% confidence interval (CI) 19–45%] for males and 22% (95% CI 8–36%) for females. For unaffected subjects, the cumulative incidence of first arterial events was 17% (95% CI 4–30%) for males and 10% (95% CI 0–20%) for females; for affected subjects who did not undergo splenectomy, the cumulative incidence of first arterial events was 2% (95% CI 0–8%) for males and 3% (95% CI 0–10%) for females.

By age 70 years, the cumulative incidence of first venous events in affected subjects who underwent splenectomy prior to age 18 years was 19% (95% CI 8–30%) for males and 20% (95% CI 6–34%) for females. For unaffected subjects, the cumulative incidence of first venous events was 12% (95% CI 1–23%) for males and 4% (95% CI 0–11%) for females; for affected subjects who did not undergo splenectomy, the cumulative incidence of first venous events was 4% (95% CI 0–13%) for males and 7% (95% CI 0–13%) for females.

Hazard ratio (HR) estimates from Cox proportional hazards regression models are provided in Table 2. Males were at greater risk of arterial events (HR 1.73, 95% CI 1.02–2.93, $P = 0.04$) than females. In contrast, risks of venous events did not differ by gender (HR 0.86, 95% CI 0.42–1.75, $P = 0.68$). Affected subjects who did not undergo splenectomy were at decreased risk of arterial events as compared to unaffected subjects (HR 0.22, 95% CI 0.08–0.52, $P = 0.002$). Affected subjects who underwent splenectomy were at greatly increased risk of arterial events as compared to affected subjects who did not undergo splenectomy (HR 7.15; 95% CI 2.81–17.2; $P < 0.0001$). The difference in risk of arterial events between unaffected subjects and affected subjects who underwent splenectomy (HR 1.56; 95% CI 0.9–2.68; $P = 0.11$) was not statistically significant. In contrast, affected subjects who underwent splenectomy were at increased risk of venous events as compared to both unaffected subjects (HR 3.00; 95% CI 1.26–7.13; $P = 0.01$) and affected subjects who did not undergo splenectomy (HR 3.33; 95% CI 1.13–9.79; $P = 0.03$). There was no significant difference in risk of venous events between unaffected subjects and affected subjects who did not undergo splenectomy (HR 0.90; 95% CI 0.26–3.12; $P = 0.87$).

Five subjects who underwent splenectomy reported additional vascular problems: leg amputation, retinal vein occlusion, acute anterior ischemic optic neuropathy, and two cases of pulmonary hypertension. We received no reports of additional vascular events from the other subject groups.

## Discussion

Several caveats should be noted regarding these data from hereditary spherocytosis families. The number of unaffected subjects in our database is smaller than would be expected for a simple Mendelian dominant defect: over several decades, more

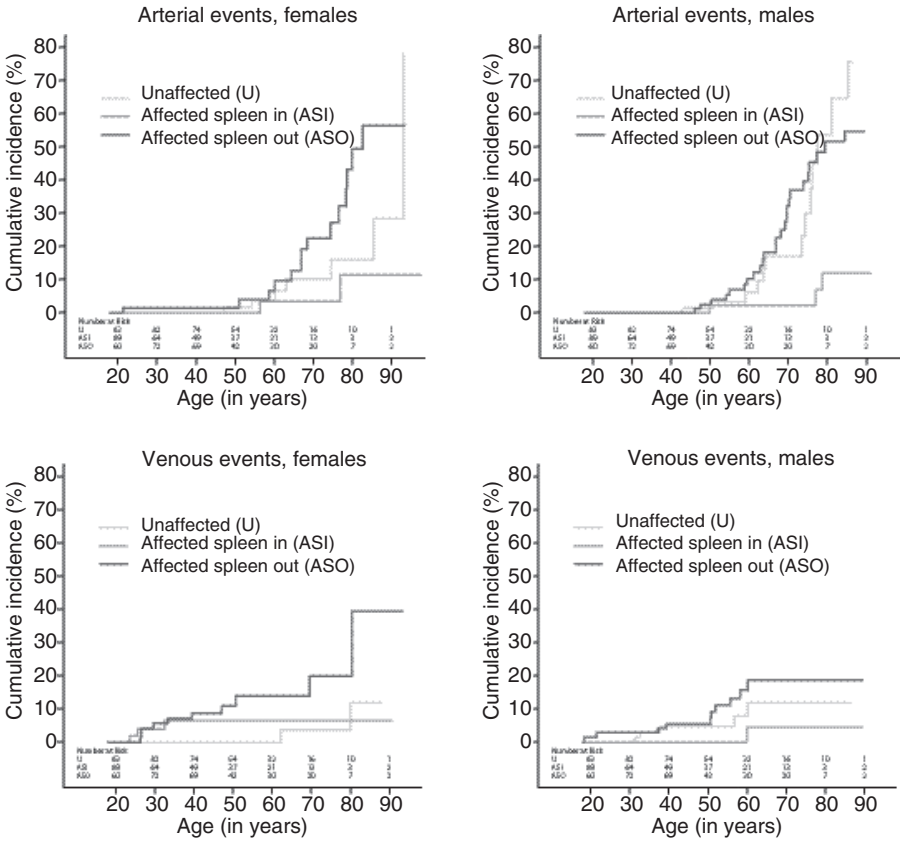


**Fig. 1.** Estimated cumulative incidence of arterial and venous events.

**Table 2** Cox proportional hazards regression models

| | Hazard ratio | 95% Confidence interval | *P*-value |
|---|---|---|---|
| Arterial events | | | |
| Male sex | 1.73 | 1.02–2.93 | 0.04 |
| Affected spleen in vs. unaffected | 0.22 | 0.08–0.58 | 0.002 |
| Affected spleen out vs. unaffected | 1.56 | 0.90–2.68 | 0.11 |
| Affected spleen out vs. affected spleen in | 7.15 | 2.81–18.2 | < 0.0001 |
| Venous events | | | |
| Male sex | 0.86 | 0.42–1.75 | 0.68 |
| Affected spleen in vs. unaffected | 0.90 | 0.26–3.12 | 0.87 |
| Affected spleen out vs. unaffected | 3.00 | 1.26–7.13 | 0.01 |
| Affected spleen out vs. affected spleen in | 3.33 | 1.13–9.79 | 0.03 |

unaffected subjects were lost to follow-up. Our earlier studies of complete sets of sibships and offspring revealed the expected 50% of affected subjects.

Some questionnaires were not returned or were incomplete, and some subjects died before we sent them a questionnaire. The majority of the data were self-reported. Some data were verified from medical records. We believe it to be unlikely that coronary surgery, carotid artery surgery and pulmonary embolus would be over-reported on a questionnaire.

We have no data about smoking or body mass index. Although we have no data about cholesterol, it is well documented that serum cholesterol is low in hereditary spherocytosis and rises after correction of anemia by splenectomy [2].

The HR for an adverse arterial event is much greater in the comparison of 'affected spleen out' to 'affected spleen in' than in the comparison of 'affected spleen out' to 'unaffected.' This is probably because the 'affected spleen in' subjects, as compared to 'unaffected' subjects, have three features associated with reduced arterial events: lower hemoglobin level [3,4], elevated bilirubin [5,6], and lower cholesterol.

As our data about adverse vascular events come only from families with hereditary spherocytosis, we searched Medline for reports of adverse vascular events occurring more than 1 month after splenectomy, regardless of the indication for surgery. We found 80 citations [1,7–85] documenting nine different, although not necessarily independent, adverse vascular events after splenectomy performed for more than 14 different indications. (A tabulation of these data is available via e-mail request to RFS.).

Although many of these 80 citations are reports of a single case or a small series of cases, some contain data gathered in a manner that provides evidence that splenectomy is accompanied by a significant, persistent, long-term risk of adverse vascular events. The five following paragraphs refer to 13

citations in which adverse vascular events were significantly more common in subjects who had had a splenectomy.

### *Arterial events*

A case control study of 740 World War II veterans [7] who had their spleen removed for trauma found a significantly increased risk (relative risk 1.85) of death from ischemic heart disease. One hundred and forty spherocytosis patients who had the spleen removed had a greatly increased rate (approximately 5-fold) of arterial events after age 40 years when compared to 88 spherocytosis patients who did not have a splenectomy [1].

### *Thromboembolic events and pulmonary embolus*

A retrospective review of 83 patients with thalassemia intermedia found that 23 of 58 persons who had had a splenectomy experienced a thromboembolic event; in contrast, only one of 25 who had not had a splenectomy had such an event [37]. An impressively large autopsy study [55] compared the incidence of pulmonary embolus in 202 adult cadavers without a spleen to that of a matched deceased group ($n = 403$) with a spleen. Pulmonary embolus was considered to be 'the major or a contributory cause of death' in 35.6% of the asplenic cases and in 9.7% of cases having a spleen.

### *Pulmonary hypertension*

Hoeper *et al.* [14] reported that seven of 61 persons receiving a lung transplant for idiopathic pulmonary hypertension had previously had a splenectomy; none of 151 persons receiving a lung transplant for other reasons had had a prior splenectomy. Bonderman *et al.* [79] compared the clinical characteristics of 109 patients with chronic thromboembolic pulmonary hypertension to the clinical characteristics of 189 patients with acute pulmonary embolism. Ten of the former had had a prior splenectomy, whereas only one of the latter had had a prior splenectomy. Jais *et al.* [68] reported that 8.6% of 257 patients diagnosed as having chronic thromboembolic pulmonary hypertension had had a prior splenectomy, whereas only 0.6% of the 180 'control' subjects had had a prior splenectomy. Singer *et al.* [80] used echocardiography to evaluate 25 thalassemic patients for pulmonary hypertension, and found it in 17 subjects, 16 of whom had had a prior splenectomy. Of the eight subjects without pulmonary hypertension, two had had a prior splenectomy. Each of two studies [46,58] of pulmonary hypertension in Gaucher disease found that the frequency of pulmonary hypertension was significantly greater in those who had had a splenectomy.

### *Priapism*

A review of 21 patients with priapism [69] found 10 patients with sickle cell disease, but three of the other 11 had had the spleen removed for trauma months or years prior to the onset of priapism. We found seven other reports of priapism after splenectomy performed for a variety of conditions [22–24,37,42,75,84].

### *Osteonecrosis*

In Gaucher disease, the prevalence of osteonecrosis is greater in those who have had the spleen removed [34,71]. A retrospective study of 51 Gaucher patients found that a patient with a splenectomy was 10 times more likely to have osteonecrosis of any of the major joints than was a patient without a splenectomy (odds ratio 10.0, 95% CI 1.7–58.4, $P < 0.01$) [34].

The causation of a significant adverse vascular event is certainly multifactorial in many instances. A prime example is the frequent occurrence of pulmonary hypertension in thalassemia. The continuing hemolysis after splenectomy done for thalassemia or stomatocytosis is a source of agents or conditions believed to contribute to the development of pulmonary hypertension [80,86,87]. These prothrombotic features would add to the prothrombotic effects of splenectomy. The literature suggests that persons with the combination of splenectomy and continuing hemolytic anemia (thalassemia [25,37], stomatocytosis [10,43,52,68,73]) are more likely to have ensuing thromboembolism or pulmonary hypertension than persons with isolated chronic hemolytic anemia. However, data comparing the incidence of adverse vascular events in comparable groups of thalassemia or stomatocytosis patients with and without a spleen are not available. Another example of multifactorial causation is the increased risk of adverse arterial events after splenectomy for hereditary spherocytosis: the increase in serum cholesterol associated with the correction of anemia is surely accepted as a significant risk. An increased hematocrit is a documented risk [3–5]. Lower bilirubin is associated with increased risk of severe coronary disease [6] and myocardial infarction [88]. Schwertner [6] found that 'a 50% decrease in total bilirubin was associated with a 47% increase in the odds of being in a more severe CAD (coronary artery disease) category. Our data suggests that serum bilirubin is an inverse and independent risk factor for CAD, with an association equivalent in degree to that of systolic blood pressure.'

It is to be noted that several of the vascular events that are more common in persons who have had a splenectomy are also more common in adults with sickle cell disease. Pulmonary hypertension, priapism and osteonecrosis are well-documented vascular hazards of sickle cell disease. The term autosplenectomy has been applied to sickle cell disease patients on the basis of evidence from autopsy, radiography and experimental studies.

There are impressive data to support the hypothesis that an immune function of the spleen retards the development of atherosclerosis in hypercholesterolemic mice [89]. We are not aware of data from humans to suggest such a role for the spleen, but the data reported here from hereditary spherocytosis families are consistent with that possibility.

## Conclusion

Data from our survey of hereditary spherocytosis family members as well as numerous reports in the literature support an association between splenectomy and increased risk of adverse arterial and venous events.

## Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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