Intramural Hematoma of the Aorta
Predictors of Progression to Dissection and Rupture
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Background—Aortic intramural hematoma (IMH) is a variant of overt aortic dissection. The predictors of progression of IMH to dissection and rupture are still unknown, and strategies for management are not established.

Methods and Results—A multicenter study was conducted comprising 66 patients with IMH and hospital admission ≤48 hours after onset of initial symptoms. Among these, progression to aortic dissection or rupture occurred in 30 (45%) and death occurred in 13 (20%) patients within 30 days. Late progression was noted in 14 (21%) and death in 11 (17%) patients, yielding a 1-, 2-, and 5-year survival of 76%, 73%, and 43%, respectively. In a set of 9 variables, multivariate analysis identified IMH location in the ascending aorta (type A; \( P = 0.02 \)) and moderately ectatic aortic diameters (49±13 mm with progression versus 57±16 mm without progression; \( P = 0.03 \)) as independent predictors of early progression. In type A IMH, early mortality was 8% with swift surgery versus 55% without surgery (\( P = 0.004 \)). The risk of late progression of IMH was independently associated with age at index diagnosis (\( P = 0.01 \)) and absence of \( \beta \)-blocker therapy during follow-up (\( P = 0.03 \)). Kaplan-Meier analysis confirmed improved 1-year survival of IMH with \( \beta \)-blocker therapy (95% versus 67% without \( \beta \)-blockers; \( P = 0.004 \)).

Conclusions—Regardless of aortic diameter, IMH of the ascending aorta (type A) is at high risk for early progression, and, thus, undelayed surgical repair should be performed. Moreover, oral \( \beta \)-blocker therapy may improve long-term prognosis of IMH independent of anatomical location. (Circulation. 2003;107:1158-1163.)

Key Words: aneurysm ● aorta ● hemorrhage ● progression ● stents

Intramural hematoma (IMH) of the aorta is a variant of overt dissection with no entry or false lumen flow.\(^1\)\(^{-14}\) However, progression of IMH both to overt dissection and rupture of the aorta is unpredictable, and strategies for therapeutic management are not established. For instance, whereas blood pressure control using \( \beta \)-adrenergic receptor blockers is widely accepted for treating IMH, surgical repair of proximal IMH (type A) is not yet recognized as therapeutic standard for prevention of serious complications.\(^1\)\(^{-14}\) Thus, this multicenter study was conducted to assess predictors of progression both early and late after diagnosis of IMH.

Methods

Patients

Between January 1994 and December 2000, patients with clinically suspected acute aortic dissection were subjected to tomographic imaging at the University Hospitals Rostock and Eppendorf, Hamburg, the Hannover Medical School, Hannover, the Christian-Albrechts-University, Kiel, all in Germany, and the University of Bologna, Italy. Initial tomographic imaging was performed by random use of transesophageal echocardiography (TEE), contrast-enhanced x-ray computed tomography (CT), and MRI. All cases with IMH on initial images were confirmed by additional tomographic modalities\(^1\)\(^{-12}\)\(^{-14}\); discordant diagnostic findings were resolved by a third independent imaging procedure in 7 patients. Imaging was completed within 24 hours of hospital admission. Thus, a total of 66 consecutive patients (41 men and 25 women; mean age±SD, 61±14 years) were identified with acute IMH.

Diagnostic Imaging

On arrival at the emergency room, TEE was performed with color and pulsed Doppler flow mapping and multiplane transducers operating at 5.0 MHz (HP 21362A; Hewlett Packard Inc) with a 0.5-inch VHS video recorder (AG-7330 E; Panasonic) and contrast-enhanced CT with third-generation scanners (Somatom Plus; Siemens AG) and bolus injections of 80 to 150 mL of nonionic contrast medium (Solutrast 300 Byk Gulden). MRI was performed with a whole body magnet operating at 1.5 Tesla (Magnetom Vision or Magnetom Symphony, Siemens AG) and an acquisition matrix of 256 by 192 phase-encoding steps.\(^12\)\(^{-14}\) IMH was diagnosed in absence of a dissecting membrane, intimal disruption, or false lumen.
flow but in presence of regional aortic wall thickness >7 mm in circular or crescent shape caused by intramural accumulation of blood.1,12–14

Medical Treatment
All patients with IMH on initial evaluation were referred to an intensive care unit.14 Invasive blood pressure monitoring was performed during administration of intravenous β-adrenergic receptor blocking agents (titrated atenolol, metoprolol, or esmolol), calcium channel antagonists, and nitroprusside sodium, isolated or in combination with nitroglycerin, to lower systolic blood pressure ≤100 to 120 mm Hg. Oral β-adrenergic receptor blockers were administered isolated (12 patients) or in combination with calcium channel antagonists, ACE inhibitors, or β-adrenergic receptor blockers; only 10 patients with β-blocker intolerance, systolic blood pressure <100 mm Hg, or noncompliance had temporal cessation of oral β-blocker intake.

Surgical Treatment
Emergent surgery was performed for contained ascending aortic rupture, cardiac tamponade, or progression to type A dissection in 15 patients for contained rupture of the descending aorta in 3 patients. Progressive enlargement ≥70 mm of the aortic root (6 patients) or persistent or recurrent severe pain syndrome (6 type A IMH, 2 type B IMH) required after surgery ≤14 days of hospital admission. Surgery of type A was not performed in 6 patients, with death in 5 patients refusing surgery and 1 elderly, multimorbid patient. Type A IMH was repaired using a composite graft with reimplantation of the coronary arteries in 6 patients and a supracoronary tube graft in 21 patients; regurgitant aortic valves were resuspended rather than replaced.15 Partial or total aortic arch replacement was performed in 12 patients for aneurysm, intimal disruption, contained rupture, or occlusion of aortic arch branches. Type B IMH was repaired by placing a tube15,16 or stent graft in the descending aorta (Figure 1).

Follow-Up
Early progression of IMH was considered present with evolution to overt dissection, aortic rupture, or aneurysm (aorta diameter at a level of IMH ≥70 mm) after ≤30 days of hospital admission. Accordingly, progression was considered late when such evolution developed beyond 30 days. Autopsy was required for assessing late progression in fatal cases. Follow-up over 31±27 months (range, 6 to 123 months) included outpatient visits and CT imaging 6 months after the index event and then in yearly intervals.

Figure 1. Serial CT images in sagittal orientation showing progression of distal (type B) IMH to overt type B dissection over 4 months (from upper left to lower left); the lower right image demonstrates an MR angiogram in identical orientation after successful stent-graft placement for reconstruction of the descending aorta.
TABLE 1. Early Mortality in Relation to Treatment and Type of IMH

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type A (%)</th>
<th>Type B (%)</th>
<th>Type A (%)</th>
<th>Type B (%)</th>
</tr>
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<tbody>
<tr>
<td>von Kodolitsch</td>
<td>5/27</td>
<td>5/15</td>
<td>13/22</td>
<td>5/64</td>
</tr>
<tr>
<td>Harris</td>
<td>0/4</td>
<td>1/7</td>
<td>2/4</td>
<td>0/4</td>
</tr>
<tr>
<td>Vilacosta</td>
<td>1/2</td>
<td>0/1</td>
<td>2/6</td>
<td>9/12</td>
</tr>
<tr>
<td>Sueyoshi</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0/9</td>
</tr>
<tr>
<td>Bolognesi</td>
<td>0/1</td>
<td>...</td>
<td>1/3</td>
<td>...</td>
</tr>
<tr>
<td>Moriyama</td>
<td>1/5</td>
<td>0/1</td>
<td>0/3</td>
<td>0/19</td>
</tr>
<tr>
<td>Kaji</td>
<td>0/9</td>
<td>...</td>
<td>1/13</td>
<td>...</td>
</tr>
<tr>
<td>Shimizu</td>
<td>0/2</td>
<td>1/6</td>
<td>3/11</td>
<td>1/32</td>
</tr>
<tr>
<td>Nishigami</td>
<td>...</td>
<td>...</td>
<td>1/8*</td>
<td>1/8‡</td>
</tr>
<tr>
<td>Song</td>
<td>1/6</td>
<td>...</td>
<td>1/18</td>
<td>...</td>
</tr>
<tr>
<td>Sohn</td>
<td>0/2</td>
<td>...</td>
<td>0/13</td>
<td>0/10</td>
</tr>
<tr>
<td>Present study</td>
<td>2/27</td>
<td>1/8</td>
<td>6/11</td>
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<tr>
<td>Total (%)</td>
<td>10/86 (12)</td>
<td>8/39 (20)</td>
<td>30/125 (24)</td>
<td>20/206 (10)</td>
</tr>
</tbody>
</table>

*Death 44 days after hospital admission. †Death 36 days after hospital admission. §P=0.012 vs medical treatment type A. ‡P=0.094 vs medical treatment of type B.

Study Variables

Nine variables were tested separately for prediction of early and late progression (Table 3). We assessed sex, age at the time of initial diagnosis, and presence of chronic arterial hypertension. Moreover, patients with clinical stigmata of inherited connective tissue disease, diagnosis of IMH under the age of 45 years, or a family history of aortic disease were assessed for presence of Marfan syndrome according to the Gent nosology. A bicuspid aortic valve was diagnosed by echocardiography or intraprostatic examination. Based on findings from at least 2 independent topographic imaging modalities, type A IMH was diagnosed when involving the ascending aorta and type B IMH was diagnosed when sparing the ascending aorta; arch IMH was counted separately. IMH was considered either localized, when confined to one aortic segment, or extended with involvement of ≥2 segments. The maximal aortic diameter was measured at the site of IMH appearance. Finally, chronic β-blockade was present with oral administration of β-adrenergic antagonists ≥6 months alone or in combination with calcium channel antagonists, ACE inhibitors, and documented normal blood pressure.

Literature Review

The English literature from 1996 to 2001 was screened for reports on outcome of IMH using MEDLINE key words aortic diseases, aorta, hematoma, and intramural hematoma and cross-references. Publications before 1997 are incorporated using results from our previous analysis; cases with penetrating aortic ulcer were excluded (Table 1).

Statistical Analysis

The risk of IMH for early and late progression was tested separately for a set of 9 variables using Mann-Whitney test for continuous data and Fisher’s exact test for categorical data. Variables with statistical significance set at P<0.05 (2-sided) were included in a multivariate logistic regression model. Estimates of risk (odd ratios) were calculated based on coefficients from the logistic models. Receiver operating characteristic (ROC) analysis was performed to assess age at diagnosis of IMH as a discriminator of increase from low risk for progression. Actuarial survival was assessed with the log-rank test for comparing Kaplan-Meier survival curves. Values were presented as mean±SD or frequencies. Statistical analysis was performed using SPSS software (SPSS for Windows, release 9.0.1).

Results

Clinical Presentation of IMH

IMH was diagnosed in 66 patients, involving the ascending aorta in 38 cases (58%) and sparing it in 28 (42%). A typical feature of proximal IMH was severe chest pain (79% in type A versus 50% in type B; P=0.02), whereas distal IMH often had upper or lower back pain (68% in type B versus 26% in type A; P=0.001); diagnostic imaging was completed within 48 hours of presentation. Widening of the mediastinum or the aortic shadow and pleural effusion on chest radiography were frequent findings in both types. Conversely, aortic regurgitation (26% in type A versus 4% in type B; P=0.02) and pericardial effusion with or without cardiac compression (50% in type A versus 3% in type B; P<0.0009) were usually associated with proximal IMH (Table 2).

Early and Late Prognosis of IMH

IMH showed signs of progression in 39 patients within 30 days of admission (59%); of these, 13 patients developed overt dissection, including contained rupture in 6 (with cardiac tamponade in 3) and malperfusion in 1 (bowel and limb ischemia). Contained rupture was not preceded by dissection in 17 patients, followed by tamponade in 8, ventricular fibrillation in 1, and paraparesis in 1 patient. Nine additional patients developed progressive aneurysm (aortic diameter ≥70 mm) and received surgery before complications. Thirteen patients with early progression (including 1...
patient with postsurgical suicide) died, reflecting an all-cause early mortality of 20%.

Late progression was observed on CT imaging in 14 of 53 survivors over 31–/H11006/27 months, with contained rupture in 11 and overt dissection in 3 cases; progression was associated with death in 11 instances. In absence of late progression, net regression (with partial reabsorption of IMH) was documented in 27 and 12 patients, respectively, on CT imaging at 6 months. Cumulative survival was 76% at 1 year, 73% at 2 years, and 43% at 5 years (Figure 2).

Predictors of Progression and Death

Proximal IMH (involving the ascending aorta) emerged as the only predictor of early progression (type A in 72% of progressive IMH versus 37% of stable IMH; odds ratio, 4.327; 95% confidence interval [CI], 1.519 to 12.331; \(P=0.006\)). Early progression was unrelated to age, sex, chronic arterial hypertension, Marfan syndrome, bicuspid aortic valve, and both local extent and diameters at the site of IMH.

Late progression of IMH was associated with younger age (49±17 versus 64±11 years in IMH without late progression; \(P<0.003\), Marfan syndrome (\(P=0.02\), and absence of \(\beta\)-adrenergic antagonists (only 7% of patients with IMH with late progression were treated with \(\beta\)-blockers compared with 49% of IMH patients without late progression; \(P=0.009\)) (Table 3).

On multivariate analysis, only younger age (OR, 0.92; 95% CI, 0.86 to 0.98; \(P=0.01\)) and absence of long-term oral \(\beta\)-blocker therapy (OR, 10.8; 95% CI, 1.2 to 96.4; \(P=0.03\)) were confirmed as independent predictors of late progression; Marfan failed to qualify as a risk predictor on multivariate analysis for numeric reasons (\(P=0.5\)).

ROC analysis identified age ≥56 years as a cutoff for better long-term prognosis (area under the curve, 0.74; 95% CI, 0.577 to 0.907; \(P=0.01\)), with a positive and negative predictive value of 74% and 65%, respectively. Actuarial survival analysis of IMH confirmed better long-term outcome on oral \(\beta\)-blocker therapy (95% versus 67% in patients without \(\beta\)-blocker treatment (\(P=0.004\); Figure 3).

Discussion

This observational study represents the largest series on outcomes of acute IMH. Most notably, 39 of 66 cases (59%) revealed evidence of progression to overt dissection, contained rupture, or aneurysm (≥70 mm diameter) within 30 days of hospital admission. Considering an early death rate of 20% and a 5-year survival of 43%, our findings are supported by the global experience in 456 cases of IMH with an early death rate of 16%, whereas 5-year survival rates are not available.1–11

In contrast to classic evolution to overt dissection, contained rupture from disintegration of outer layers of the aortic media developed in 17 of 39 patients as another form of IMH progression (43%). Moreover, 9 patients developed aneurysm at the site of IMH and had surgical repair before dissection or rupture (23%). Like in overt dissection, widening of the mediastinum or the aortic shadow, pleural effusion and pain,

| Table 3. Univariate Analysis of Progression of IMH |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Early Progression | Late Progression | 
|                 | Present (N=39)   | Absent (N=27)   | Present (N=14)  | Absent (N=39)   | 
| Male            | 25/16           | 0.8             | 7/26            | 0.3             |
| Age at IMH, y   | 59±16           | 64±8            | 0.3             | 49±17           | 64±11           | 0.003           |
| Arterial hypertension | 28/21           | 0.8             | 11/28           | 0.7             |
| Marfan syndrome | 3/0             | 0.3             | 3/0             | 0.02            |
| Bicuspid aortic valve | 0/2             | 0.2             | 1/1             | 0.5             |
| Type A IMH      | 28/10           | 0.006           | 10/20           | 0.2             |
| Localized IMH   | 20/11           | 0.3             | 8/19            | 0.7             |
| Aortic diameter, mm | 56±18           | 49±8            | 0.17            | 59±19           | 54±13           | 0.7             |
| Absence of long-term \(\beta\)-blocker treatment | ...            | ...             | 13/20           | 0.009           |

* Early progression indicates progression of IMH <30 days of hospital admission; late progression, progression of IMH >30 days of hospital admission. Variables are defined in Methods.
aortic regurgitation, and pericardial effusion may emerge after initial IMH, whereas focal neurological signs or malperfusion syndrome are incidental. Hence, the subtle initial pathology of IMH is more likely to be missed than overt dissection.

**Prediction of Early Progression**

For the first time, proximal location of IMH was confirmed as an independent predictor of progression to dissection, contained rupture, or aneurysm formation. However, proximal (type A) IMH was no longer related to early death, because surgical repair was performed in most cases of the current series. The high risk of a nonsurgical approach in type A IMH, however, is reflected in the 55% rate of early mortality with medical treatment compared with 8% with surgical repair (P=0.004; Table 4). Considering a 12% early mortality after surgery and a 24% death rate with medical treatment, global experience confirmed a trend to better outcome after surgery of proximal IMH (P=0.12; Table 1).

Interestingly, some Asian series reported low death rates in proximal IMH with medical therapy. However, in fact, 10 of 22 type A IMH (45%) needed early surgery between 7 and 13 days of diagnosis and 4 cases developed cardiac tamponade requiring pericardiocentesis before medical treatment. Cardiac tamponade was also observed in 2 of 3 type A IMH patients subjected to medical management, whereas death was reported in 3 cases of proximal aortic involvement. Nishigami et al reported 8 cases of medically treated type A IMH with 7 survivors; yet IMH requiring surgery and cases with aortic diameters >55 mm or cardiac tamponade were excluded from this analysis. Similarly, in a series of 18 type A IMH treated medically, 1 patient died in shock and 4 required emergent pericardiocentesis or surgery for development of aortic dissection. Thus, the Asian experience may attribute a more benign prognosis under medical management of type A IMH but fails to challenge findings of proximal IMH in the white race, frequently progressing to serious complications (Table 1).

Moreover, Kaji et al observed better prognosis of proximal IMH with aortic diameters <50 mm. Similarly, aortic diameters tended to be smaller in stable compared with progressive IMH (49±8 versus 56±18 mm in progressive IMH; P=0.17). However, 20 of 37 cases with aortic diameters <50 mm eventually progressed to dissection or rupture (54%); thus, IMH with normal to moderately enlarged aortic diameter (usually from intramural blood at the expense of luminal width) does not preclude progression.

**Prediction of Late Progression**

β-Adrenergic blocking agents are effective in the management of overt aortic dissection and in retarding progression of aortic root aneurysm in Marfan syndrome and abdominal aneurysm. Such agents protect the aorta by reducing both systolic pressure and the rate of change in central arterial pressure and, presumably, by chemical effects on the extracellular matrix of the aorta. Thus, our finding that effective oral β-blocker therapy infers a reduced rate of late progression is novel but not unexpected in IMH, considering the beneficial impact of vigorously lowering the driving force for dissection.

The observation that older age (>56 years) at initial diagnosis of IMH is related to better long-term prognosis may be explained by more focal microscars along the aortic wall inherently limiting a longitudinal extension of IMH. Accordingly, favorable outcomes of IMH are consistently reported in patients beyond 65 years. Thus, considering both advanced aortosclerosis with increasing age and the lower risk of progression, a conservative strategy (with β-blockade and serial imaging) may be justified in elderly multimorbid patients.

**Conclusions**

IMH of the aorta is a potentially lethal disorder with frequent progression to aortic rupture, dissection, or aneurysm. Short-term prognosis is serious in IMH involving the ascending aorta, and surgical repair improves outcome regardless of the aortic diameter. IMH confined to a single aortic segment or...

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**TABLE 4. Survival of IMH in Relation to Type and Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Type A IMH</th>
<th>Arch IMH</th>
<th>Type B IMH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgical</td>
<td>Medical</td>
<td>P</td>
</tr>
<tr>
<td>Early survival (%)</td>
<td>25/27 (92)</td>
<td>5/11 (45)</td>
<td>0.004</td>
</tr>
<tr>
<td>Late survival (%)</td>
<td>19/25 (76)</td>
<td>3/5 (60)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Arch indicates aortic arch; numbers indicate surviving patients per subgroup.
aortic diameters <50 mm may not exclude early progression in the white race. Late survival of IMH is not benign, yet late progression is not predicted by location of IMH or width of the aorta nor by presence of risk factors. Long-term prognosis, however, may benefit from chronic β-blockade for blood pressure control irrespective of surgical repair.

References
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