Italian multicentre study on type A acute aortic dissection:
a 33-year follow-up†

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Abstract

OBJECTIVES: Despite substantial progress in surgical techniques and perioperative management, the treatment and long-term follow-up of type A acute aortic dissection (AAD) still remain a major challenge. The objective of this retrospective, multicentre study was to assess in a large series of patients the early and long-term results after surgery for type A AAD.

METHODS: We analysed the preoperative, intraoperative and postoperative conditions of 1,148 consecutive patients surgically treated in seven large referral centres from 1981 to 2013. We applied to each patient three different multi-parameter risk profiles (preadmission risk, admission risk and post-surgery risk) in order to compare risk factors and outcome. Long-term Kaplan–Meier survival was evaluated.

RESULTS: The median age was 64 years and the male population was predominant (66%). Identified diagnosis of collagen disease was present in 9%, and Marfan syndrome in 5%. Bicuspid aortic valve was present in 69 patients (6%). Previous cardiac surgery was identified in 10% of the patients. During surgery, the native aortic valve was preserved in 72% of the cases, including leafllet resuspension in 23% and David operation in 1.2%. Considering aortic valve replacement (AVR: 28%), bioprosthesis implantation was performed in 14.7% of the subjects. Neurological impairment at discharge was shown in 23% of the cases among which 21% of patients had new neurological impairment versus preoperative conditions. The overall 30-day mortality rate was 25.7%. All risk profiles remained independently associated with in-hospital mortality. During the available follow-up of hospital survivors (median: 70 months, interquartile range: 34–113, maximum: 396), cardiac-related death occurred in 7.9% of the subjects. The cumulative survival rate for cardiac death was 95.3% at 5 years, 92.8% at 10 years and 52.8% at 20 years. Severe aortic regurgitation (AR) (grade 3–4) at the time of surgery showed to be a significant risk factor for reintervention during the follow-up (P < 0.001). Among risk profiles, only the preadmission risk was independently associated with late mortality after multivariate analysis. Unexpectedly, there was no difference in freedom from cardiac death between patients with and without AVR.

CONCLUSIONS: Although surgery for type A has remained challenging over more than three decades, there is a positive trend in terms of hospital mortality and long-term follow-up. About 90% of patients were free from reoperation in the long term, although late AR remains a critical issue, suggesting that a thorough debate on surgical options, assessment and results of a conservative approach should be considered.

Keywords: Acute aortic dissection • Prognosis • Aortic valve • Aortic prosthesis • Aortic surgery

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INTRODUCTION

Stanford type A acute aortic dissection (AAD) is an emergency situation in cardiac surgery associated with a high-risk mortality rate due to aortic rupture or malperfusion [1–4]. Over the decades, there have been improvements in diagnosis appropriateness and celerity, as well as surgical approach, particularly with regard to cerebral protection during surgery [5, 6]. However, such surgical and anaesthesiological refinements have not been clearly investigated in the very long-term period. In addition, owing to the heterogeneous populations, the different clinical statuses and presentation, the considered operations make difficult the comparison across studies, especially with reference to limited patient populations and single-centre experiences. Our multicentre study aims to evaluate whether surgical treatment of type A AAD has shown clinical outcomes in terms of in-hospital mortality in different time periods, long-term survival and freedom from reoperation.

METHODS

Patient population

After approval by local Ethical Committees, we retrospectively analysed 1148 consecutive patients surgically treated for primary type A AAD between 1981 and 2013 in seven large referral cardiac surgery centres in Italy.

Definitions

Type A AAD was defined as dissection involving the ascending aorta, within 2 weeks from onset of symptoms, systemic hypertension on the patient’s history, regardless of absence of therapy or specific medications, diabetes as a history of diabetes mellitus, or regardless of the need for oral medications or insulin. Chronic renal insufficiency was defined as a serum creatinine >2.0 mg/dl or dialysis. Familiar acute aortic events were considered including all acute aortic syndromes that occurred in patients’ relatives or parents. Acute neurological impairment was defined on the basis of the presence of any kind of acute neurological deficit. Acute myocardial ischaemia was defined by acute electrocardiographic changes or specific myocardial enzyme release. Cardiogenic shock was defined as systolic blood pressure <80 mm/Hg, secondary to cardiac tamponade, myocardial ischaemia/infarction or severe aortic insufficiency. Postoperative acute neurological impairment was defined on the basis of the presence of any documented new neurological deficit. Postoperative renal failure was defined as one of the following: (i) an increase in serum creatinine to >2 mg/dl and/or >2-fold increase in the preoperative creatinine level; (ii) need of postoperative dialysis. Malperfusion syndrome was defined as acute perfusion deficit, mesenteric or peripheral. Hospital mortality includes all deaths that occurred during the hospitalization for surgery (even if death occurred after 30 days from surgery) and deaths that occurred after discharge but within 30 days. Late cardiac mortality includes all deaths due to acute myocardial infarction, chronic heart failure, malignant arrhythmia, cardiovascular reoperation or sudden unexplained death.

Surgical techniques

Arterial access for cardiopulmonary bypass (CPB) institution was achieved through the femoral artery in 72% of the cases, and through the axillary artery in 16.7%. Venous drainage was accomplished by cannulation of the right atrium–inferior vena cava in 68% of the patients. In only 4% of patients CPB was initiated prior to sternotomy due to severe haemodynamic instability. Organ protection during the circulatory arrest phase was achieved with different levels of hypothermia [median: 22°C, interquartile range (IQR): 18°–25°C]. Cerebral protection was accomplished with retrograde venous cerebral perfusion in 300 patients, with moderate hypothermia and selective direct antegrade perfusion of supraaortic vessels in 502 patients, and the remaining 346 patients were treated with lone deep hypothermic circulatory arrest [7–9].

Follow-up

The follow-up data were collected by an active search of charts from outpatient clinics, by phone contacts with referral cardiologist or general practitioners, by phone call to patient or family. For patients who died during the follow-up, the date of death was recorded. The survival follow-up was closed on 30 April 2014.

Statistical analysis

Extracted database variables were tabulated using Microsoft Excel® (Microsoft Corp, Redmond, WA, USA) and statistical analysis was computed using SPSS, release 13.0 for Windows® (SPSS, Inc., Chicago, IL, USA). Continuous variables are expressed as mean and median with IQR. Discrete variables are presented as frequency percent. Differences between groups were compared using Student’s t-test and the χ² test, as appropriate. Univariable ordinal logistic regression analysis was used and results are presented as odds ratio (OR) and their 95% confidence interval (CI). Significant variables (P < 0.1) were entered in the final multivariable model. Kaplan–Meier univariate unadjusted survival estimates were calculated and compared using a log-rank test. The individual effect of variables on survival was evaluated by Cox proportional-hazards regression analysis. Multivariate hazard ratios (HRs) are presented along with their 95% CIs.

Finally, in order to find a preliminary correlation between risk factors and outcome, we designed three different multiparameter risk profiles, assessing a patient as affected with at least three parameters positive from each profile:

(i) **Preadmission risk (PAR):** age ≥70 years, female gender, systemic arterial hypertension, Marfan syndrome, family history for acute aortic disease, diabetes, renal insufficiency, previous cardiac disease or surgery

(ii) **Admission risk (AR):** acute neurological impairment, anisocytosis, myocardial ischaemia or infarction, mechanical ventilation at admission, cardiac arrest, cardiogenic shock, acute renal insufficiency, pericardial effusion, coronary disease (if preoperatively assessed)

(iii) **Post-surgery risk (PSR):** postoperative neurological complications, respiratory insufficiency, low cardiac output syndrome requiring inotropes, acute renal failure, systemic malperfusion.
RESULTS

Data on demographic variables, clinical characteristics, type of operation and postoperative outcomes were retrospectively retrieved from the institutional database (Tables 1–3).

Hospital outcome

In-hospital complications occurred in 59% of patients. One complication occurred in 26%, 2 in 19% and ≥3 in 14%. A neurological impairment was observed in 264 (23%) of the patients, among whom 21% of patients had new neurological impairment versus preoperative conditions. Renal failure occurred in 207 (18%) among whom 10% had a new onset; peripheral malperfusion syndrome occurred in 103 (9%).

Hospital mortality rate was 25.7% (n = 295) and was significantly associated with the presence of the above risk profiles: PAR 56.4 vs 24.6% (P = 0.0001, in dead and survivors, respectively); AR 20.6 vs 8.4% (P < 0.01); PSR 47.6 vs 15.3% (P < 0.001). All risk profiles remained independently associated with in-hospital mortality at the multivariate analysis (Table 4).

Preoperative and intraoperative management appeared more homogeneous and standardized among different centres starting from 2000. With reference to the temporal interval before/after 2000, hospital mortality revealed significant differences.

Patients operated on or before 2000 showed a higher hospital mortality compared with those operated later on (33.5 vs 24%, P < 0.01). Interestingly, patients treated after 2000 were significantly older than the previous ones (59.7 ± 12.9 vs 62.6 ± 12.6; P < 0.01). However, no difference in the prevalence of risk profiles (PAR, AR and PSR) were observed between the two period groups.

Long-term follow-up: all-cause mortality and cardiac-related death

There were 853 patients who were discharged alive. The follow-up had a median of 70 months (IQR: 34–113; maximum 396) and was completed in 749 (87.9%) patients, whereas 104 (12.1%) were lost at clinical contact or in local demographic registries.

The all-cause mortality rate was 25.8% (n = 193; Fig. 1). The cumulative survival rate was 83.9% at 5 years, 70.7% at 10 years and 27.8% at 20 years. Long-term survival was worse in patients over 70 years at the onset of AAD (P < 0.001) and in female patients (P < 0.001). All risk profiles affected also the long-term follow-up in univariate analysis (P < 0.001 for all); but in multivariate analysis only PAR was independently associated with late mortality (P < 0.01; HR = 3.99, 95% CI: 1.75–9.07).
The cause of death was cardiac-related in 52 patients (7.9%), namely 13 (2%) due to cardiac disease, 25 (4%) sudden death, 9 (1%) aneurysmal rupture and 5 (1%) during reintervention. Non-cardiac-related deaths occurred in 55 (8.3%) patients, and unknown in 87 (9.6%) patients. Cardiac death-related survival (Fig. 2) was 95.34% at 5 years, 92.8% at 10 years and 52.8% at 20 years, respectively. No difference in freedom from cardiac death between patients with and without aortic valve prosthesis was registered \((P = 0.96; \text{Fig. 3})\).

**Reoperation**

Reoperations at the proximal (4.4%) or distal (6.4%) aorta occurred in 81 patients (10.8%) over a median of 64 months (IQR: 29–108) from surgery. Among patients with preserved native aortic valve \((n = 522)\), 19 patients (3.6%) underwent reoperation for aortic valve insufficiency over a median follow-up of 71 months (IQR: 33–118). Comparing rates of reoperation, the group of patients with preoperative aortic regurgitation (AR) grade 3–4 at the time of AAD surgery had a higher incidence of surgical reintervention for aortic valve dysfunction \((P < 0.001; \text{Fig. 4})\).

**DISCUSSION**

In our multicentre study we analysed the early and long-term results of patients operated on an emergency basis for type A AAD. To our knowledge, this is one of the longest and largest follow-ups reported in patients operated on for such pathology.
The main issues in this acute disease remain high hospital mortality and long-term outcome.

According to the literature, the reported operative mortality rate of type A AAD repair ranges from 15 to 30% [10]. In our experience, the hospital mortality rate in the whole group was 25.7%. These results, therefore, are in accordance with the data reported in other studies and confirm the extremely high operative risk in this setting [11–16].

In particular, hospital mortality was significantly related to high-risk profiles defined on the basis of contemporary presence of known preoperative and perioperative risk factors [14–17]. Associated chronic diseases, severe clinical preoperative status at hospital admission and complications after surgery were confirmed, in multivariate analysis, as risk factors for hospital death.

Mortality rate declined in more recent decades, as shown by other series [17], notwithstanding an older age of surgically treated patients. Although more complex analyses are to be performed on this topic, advances in diagnostic and surgical management, more expeditious operations in recent era, and enhanced periand postoperative patient surveillance could justify better results with no simultaneous decrease in prevalence of risk profiles.

Nevertheless, although we could expect further decline in mortality over time, unchangeable high-risk factors in type A AAD surgery might still negatively affect results.

Regarding the long-term results, patients with type A AAD are reported with a significant reduction in survival compared with age- and gender-matched controls [18]. Our findings demonstrated that long-term survival was poorer in patients older than 70 years and in female patients, as confirmed by
other investigators [17, 19]. Furthermore, the three high-risk profiles, presented here, significantly correlated with long-term survival, in particular the chronic one. All these variables should be taken into account for surgical management and postoperative outcome.

Interestingly, incidence of cardiac death in our series was very low and did not significantly affect the long-term survival. As the matter of fact, all the reporting centres have a policy of strict postoperative follow-up and timely reoperation, if required, in patients operated for type A AAD. Obviously, this approach might have accounted for low rates of post-discharge cardiac mortality and morbidity but it cannot fix the poor postoperative prognosis related to pre-existing illness or perioperative risk profiles.

Late reoperations after type A AAD repair are relatively common with an average reoperation rate of 5.4–18% [20–22]. Although the primary objective remains patients’ survival to hospital discharge, the choice of procedure on the aortic valve should also take into account the potential risk of reoperation and the actual long-term survival of these patients. Basically, there are two options: a conservative approach with native valve resuspension or sparing operation and a more aggressive approach with aortic valve replacement with or without aortic root replacement. Saczkowski et al. [23], in a recent meta-analysis, reported a rate for aortic valve reintervention after initial conservative surgery of 2.1%/patient-year because of recurrent aortic insufficiency. The composite rate of thromboembolism and bleeding was 1.4%/patient-year in patients who had undergone an initial aortic valve replacement. The authors concluded that patients surviving a type A AAD operation have a limited long-term survival. Preservation and repair of the aortic valve is associated with a moderate risk of reoperation, but a lower risk of thromboembolism, bleeding and endocarditis.

Conversely, Wang et al. [18] and Halstead et al. [24] have demonstrated no difference in long-term survival in patients treated with either a conservative or more aggressive surgical approach. The same authors did not find any difference in the freedom from reoperation on the aortic root or valve among different types of operations.

In our analysis, survival was similar in patients operated on either with native aortic valve resuspension or aortic valve replacement. In our patient population most of the aortic valve repair was performed by simple commissural resuspension and the rate of reoperation for postoperative aortic valve dysfunction was very low, just 3.6%. Therefore, a simple and fast conservative approach to the aortic valve should always be considered in case of acute aortic insufficiency in type A AAD surgery.

Indeed, we do not know exactly the rate and the severity of late recurrent aortic insufficiency, by echo assessment. Therefore, the incidence of recurrent aortic insufficiency may be apparently underestimated. Reoperation in this setting is complex and risky. The indication for redo surgery varies in different reporting institutions and the low reoperation rate can be misleading in terms of recurrent aortic valve dysfunction.

In our study, freedom from valve reoperation with preoperative acute aortic insufficiency grade ≥3 was poorer, suggesting that a preoperative severe derangement of the aortic valve represents a risk factor for recurrent aortic insufficiency after aortic valve preservation.

Finally, considering the similar survival in patients operated either with native aortic valve resuspension or aortic valve replacement, the exact role of more complex repair of a dysfunctional aortic valve still remains to be defined, in this set of severely ill patients, particularly in patients with risk factors of failure such as bicuspid aortic valve, root enlargement, Marfan syndrome or pre-existing aortic valve dysfunction [18].

Limitations of the study

Limitations of a retrospective multicentre series affected our study. Biases are basically related the policies of different institutions and the evolving surgical approach to type A AAD. Several differences among single institutions, surgeons and different eras in terms of preoperative diagnostic management, intraoperative strategy, surgical technique and indication to reoperation could be affecting outcome. The impact of this variability was obviously not evaluated in consideration of the retrospective nature of our study. Furthermore, particularly in the first phase of the series, due to lack of intraoperative echo assessment, results of resuspension of the aortic valve could not be tested. Therefore, in some case of recurrent AR it is extremely difficult to ascribe that either to intraoperative failure or to late evolution of aortic bulb disease. Therefore the results of this study cannot be generalized to all cases of type A AAD surgery. Further study and analysis on larger patient populations are necessary.

CONCLUSIONS

Surgery for type A AAD remained challenging over more than three decades. Despite a positive survival trend in the most recent era, hospital mortality still remains high, mainly related to age, gender, pre-existing conditions, severity of clinical status at onset and perioperative complications. These factors also influence long-term survival. Aortic valve replacement in comparison with conservative procedures does not appear to worsen early and late patient prognosis. Simple aortic valve resuspension seems to be effective in the very long-term period.

Conflict of interest: none declared.

REFERENCES

Repair of acute type A aortic dissection: moving towards a more aggressive approach but keeping the old gold standards

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In this issue of the European Journal of Cardio-Thoracic Surgery, Russo et al. [1] report the early and long-term results after surgery for type A acute aortic dissection (TA-AAD) in a retrospective multicentre study from seven different Italian referral centres. They