Improving risk stratification of moderate aortic stenosis

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Background: The clinical course of patients with moderate aortic stenosis (AS) remains ill-defined. While a watchful waiting approach is advocated by international guidelines, several studies suggest that the long-term prognosis of these patients is worse than previously considered and may even be similar to patients with severe AS. Whether these findings reflect a subgroup of moderate AS with a high comorbid burden or rapid progression to severe AS is not known.

Purpose: This study sought to 1) analyze the clinical course of AS throughout all stages of the disease, 2) unveil different trajectories of progression through clustering analysis, 3) explore their impact in all-cause death.

Methods: Patients with mild to severe AS in seriated echocardiograms (TTE) were retrospectively identified after excluding for abnormal flow conditions. Aortic peak velocity (APV) was used to monitor disease progression. A sigmoid function was used to model APV throughout time. Individual acceleration rates coefficients were calculated using random-effects models and patients were then clustered into rapid (RP) and slow progressors (SP).

Results: This study included 914 patients (age 76 ± 8 years, 52% female, median follow-up time 6.8 years). 483 patients were clustered as RP (53%) and 431 as SP (47%) based on their individual acceleration rate coefficients (core parameter of sigmoid model). Since the core parameter is constant throughout time and evaluations, only two consecutive TTEs per patient are needed to calculate the acceleration rate coefficient. The time interval required between these seriated TTEs varies between 9 and 14 months. No clinical variables were consistently associated with each cluster. When comparing mortality hazard rates for SP with RP across the range of APV, we found that rapid progression was persistently associated with excess mortality (HR 1.35, CI [1.07-1.69]; p = 0.01; after adjusting for demographics, comorbidities, baseline AS severity, and time-dependent aortic valve replacement [AVR]). Using the upper limit of the mortality rate of a SP with an APV of 4 m/s as a reference, we found that a RP significantly exceeded this threshold with an APV velocity of only 3.2 m/s. We built a predictive model which incorporated the AS progression on top of guideline-derived AVR triggers to assign patients with a predicted probability of death ≥ 50% at 5 years to AVR. Using this model, we estimated that an extra death can be prevented for every 100 patients treated without exposing more patients to unnecessary AVR.

Conclusion: We identified two clusters of AS progressors, based on APV from two consecutive TTEs. RP displayed higher mortality rates across all the range of APV which can explain why same patients with moderate AS have a dismal prognosis. Since RP patients have excess adverse outcomes in early stages of AS (moderate AS), a lower APV threshold may be required to better reflect the prognosis of AS and trigger treatment.
Spline curves representing the relative risk of excess mortality of RP compared with the estimated mortality of SP. The y-axis represents the relative risk of excess mortality with a reference risk of 1 as the upper confidence limit of mortality of SP with an aortic peak velocity of 4 m/s, where risk >1 indicates excess mortality. Effect of rapid progression expressed as hazard ratio (HR) (red line) with 95% confidence intervals (CIs) (red shaded area) adjusted for age, gender, comorbidities, and time-dependent AVR. The salient point of this graph is that, when we compare the mortality of RP with SP, a lower aortic peak velocity threshold may better reflect the severity of AS (RP with an aortic peak velocity of 3.2 m/s has a lower confidence limit of mortality similar to the reference risk). RP = Rapid Progressors; SP = Slow Progressors; AS = Aortic Stenosis.