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Editorial

Crossing the Boundaries of Treatment of Valvular Heart Disease in Patients With Liver Cirrhosis

THE FIRST REPORT of transcatheter aortic valve replacement (TAVR) dates back to 2002, when Cribier et al.[1] managed to replace the aortic valve of a nonoperable 57-year-old patient with severe aortic stenosis in whom a valvuloplasty showed to be inefficacious. Through an antegrade transseptal approach, the team accomplished a good hemodynamic result with parallel patient clinical improvement. However, 4 months postprocedure, the patient died because of complicated lower limb ischemia. Paniagua et al.,[2] in 2005, published the first retrograde TAVR experience in a 62-year-old with severe aortic stenosis and good immediate result but, yet again, the patient unfortunately died on day 2.

In the last 2 decades, structural interventional cardiology has experienced an unprecedented expansion in contemporaneous medicine, revolutionizing the treatment of valvular heart disease. To date, numerous patients worldwide have benefited from the minimally invasive transcatheter approach to treat lesions that had no possible curative treatment a few decades ago. The initial case reports have evolved into robust evidence from clinical trials[3,4] and practice guidelines[5,6] to frame the role of the transcatheter approach for severe aortic stenosis, secondary mitral regurgitation, and tricuspid regurgitation, based on clinical, anatomic, and procedural factors. Surgical risk assessment scales, such as the EuroSCORE II or Society of Thoracic Surgeons score, are accepted tools to decide best patient treatment. Surprisingly enough, liver disease only appears in the Society of Thoracic Surgeons risk score as a dichotomous "yes/no" variable, which does not take into consideration the severity of liver disease. Additionally, the incidence of obesity-related liver disease in the form of nonalcoholic steatohepatitis or nonalcoholic fatty liver disease seems to be trending upward in the past years. In the United States, prevalence of liver cirrhosis (LC) is 0.27%, and represents 1.2% of all deaths, with similar figures in Europe of 0.83% and prevalence and 1.8% of all yearly deaths.[7,8] Most remarkably, both nonalcoholic steatohepatitis and nonalcoholic fatty liver disease are associated with atherosclerotic cardiovascular and valvular disease such as aortic valve disease and mitral valve calcification.[9,10]

It may be reasonable to foresee an increment in the number of patients with LC in catheterization laboratories, along with an increase of subjects on the liver transplant (LT) waiting list who have undergone a transcatheter intervention of a heart valve. Prior to consolidation of transcatheter valvular heart interventions, patients with severe valvular heart disease and LC were forced to undergo either surgical strategies or a conservative noncurative medical approach. Descriptions of cardiac surgery prior to LT or concomitantly estimated a mortality of >60% in Child-Pugh (CP) B and C.[11,12]

Therefore, the narrative review by T Ahmed entitled "Transcatheter Interventions for Valvular Heart Diseases in Liver Cirrhosis Patients" was indispensable.[13]

Evidence of Transcatheter Interventions in Patients With Liver Cirrhosis

Surgical aortic valve replacement (SAVR) before LT can be proposed only in CP-A patients, due to a bad prognosis in CP-B or C.[12] Few cases of simultaneous valve replacement with CP-B and LT have been reported, but the extremely challenging procedure should be reserved for very select patients.[14]

Randomized controlled trials of patients undergoing TAVR with LC are lacking, and most of the data were obtained from observational studies.[15,16] Nevertheless, it seems that all data showed that TAVR compared to SAVR was associated to lower odds of in-hospital mortality, blood transfusions, and hospital length of stay.[16] Despite the minimally invasive nature of TAVR, it is still associated with periprocedural complications (eg, acute kidney injury, hepatic encephalopathy, bleeding) and a 2-year mortality of >80% for high CP classes[17] unless patients were bridged to LT. Additionally, patients with CP-B or C, especially in combination with renal impairment, had a very low survival rate.[17] An optimal antithrombotic regimen and risk of valve thrombosis and infective endocarditis need to be studied in further prospective studies.

Transcatheter mitral valve interventions in LC are far less studied than TAVRs, with only a few anecdotical reports.[18,19] Compared to a surgical approach, transcatheter edge-to-edge repair in patients with LC was associated with lower in-

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hospital mortality, transfusion, length of stay, and prolonged mechanical ventilation in a recently published retrospective study.[18]

Regarding transcatheter tricuspid valve interventions, there is still less knowledge in the LC population, with only a few publications reporting improvement of liver function after transcatheter tricuspid valve interventions.[20,21]

Cardiovascular Assessment in Patients With Liver Cirrhosis

Whereas mild-to-moderate valvular heart diseases are usually well-tolerated during the surgical procedure, severe valvular heart diseases preclude liver transplant in most centers. Severe or symptomatic aortic stenosis, if not corrected, precludes the LT, due to severe hemodynamic instability, critically reduced myocardial perfusion, and poor postoperative outcome.[22] Cardiovascular complications are the most important cause of early death, and one of the most frequent causes of long-term death after LT.[23]

An LT candidate quite often presents with the peculiar cardiovascular profile associated with end-stage liver disease (ESLD), namely, high cardiac output, low systemic vascular resistance, and splanchnic vasodilatation. The more severe the liver condition, the more pronounced are the cardiovascular alterations. During LT, the patient may have to tolerate periods from minutes to hours of tachycardia, severe hypotension, acute blood loss, extreme anemia, markedly reduced venous return, and prolonged and refractory vasoplegia after reperfusion of the graft. On the contrary, consequences of massive hemoderivates transfusion or fluid administration include risk of acute right or left ventricular failure overload in the various phases of the transplant. To survive such a stressful scenario, appropriate or even better-optimized cardiovascular performance status is encouraged.[24]

Consensus on a standardized pre-LT cardiovascular evaluation and risk stratification is, to date, still lacking. Regarding symptomatic diseases, the pathways are quite well-defined; in an asymptomatic candidate, risk assessment is variable if not controversial. However, transthoracic echocardiography (TTE) is recommended in all patients by all scientific societies.

Aortic stenosis results in left ventricular pressure overload with compensatory ventricular hypertrophy and decreased left ventricular compliance. These hemodynamics are exaggerated during LT because of profound fluid shifts, resulting in a sudden decrease in preload during liver resection and impaired myocardial contractility during the postreperfusion syndrome. Transthoracic echocardiography is an important preoperative diagnostic method for evaluating the severity of aortic stenosis, but it requires careful interpretation in patients with ESLD. As a result of high transvalvular flows because of hyperdynamic circulation, reliance on aortic valve gradients alone may result in overestimation of the degree of obstruction, and the calculation of aortic valve area with the continuity equation is essential. Although additional echocardiographic findings, such as left ventricular hypertrophy, can support the diagnosis of advanced aortic stenosis; it also can be present in cirrhotic cardiomyopathy. When doubts in TTE findings arise, cardiac catheterization might be performed to assess the hemodynamic severity.[25] Additionally, the evaluation of aortic valve calcium by the Agatston score by cardiac computed tomography scanning could help to better define the severity of the disease evaluated by TTE.[26]

Hemostatic Management

The current view on hemostasis does not support the need to correct abnormalities in the coagulation system in patients with LC undergoing invasive procedures. They frequently experience substantial alterations in their hemostatic system that are apparent during screening with basic tests of hemostasis (mainly international normalized ratio, activated partial thromboplastin time, and platelet count). Historically, these changes were thought to induce a hemostasis-related bleeding tendency. Nowadays, however, it is well-accepted that the basic aforementioned hemostasis tests do not truly represent the hemostatic system operating in patients with liver disease who remain in hemostatic balance. Both pro- and antihemostatic systems change simultaneously in patients with compensated LC. Furthermore, it also is acknowledged that although patients with liver disease may experience bleeding complications, many of these bleeds are unrelated to hemostatic failure and are instead a consequence of portal hypertension or mechanical vessel injury, which could be caused by an inadvertent vessel puncture during invasive procedures.

Percutaneous cardiac interventions belong to the group of high-bleeding risk procedures, with a reported bleeding rate $>1.5\%$, in which the consequences of bleeding may result in severe detrimental sequelae, or when bleeding cannot be easily managed with local hemostatic maneuvers. In this context, accidental lesion to femoral vessels, with formation of either retroperitoneal hematoma or groin hematoma, may occur during transcatheter procedures, in addition to tamponade due to eventual myocardial/grand vessel perforation. The recent *Clinical Practice Guidelines on Prevention and Management of Bleeding and Thrombosis in Patients With Cirrhosis,* authored by the European Association for the Study of the Liver, states that, in patients with cirrhosis undergoing invasive procedures associated with a high risk of bleeding, the use of traditional hemostasis tests or viscoelastic tests of hemostasis is generally not indicated to predict postprocedural bleeding, although it may serve to provide a baseline status of the patient and to assist the physician in the case of bleeding events.[27] Furthermore, correction of a prolonged international normalized ratio with fresh frozen plasma is no longer recommended, and neither is the use of prothrombinic complex concentrates, nor the correction of fibrinogen deficiency to decrease the rate of procedure-related clinically relevant bleeding in this population. Lastly, the systematic use of tranexamic acid also is discouraged.[27]

Regarding thrombocytopenia, the prophylactic infusion of platelet concentrates or use of thrombopoietin-receptor (TPO-R) agonists, are not recommended when platelet count is more than 50×109/L or when bleeding can be treated by local hemostasis. When local hemostasis is not possible and the platelet count is between 20 × 109/L and 50 × 109/L, the infusion of platelet concentrates or TPO-R agonists should not be routinely performed but may be considered on a case-by-case basis. When local hemostasis is not possible and platelet count is very low (<20 × 109/L), the infusion of platelet concentrates or TPO-R agonists should be considered on a case-by-case basis.[27] Besides that, the ability of the prophylactic hemoderivated transfusion has never been proved. On the other hand, blood product transfusion may be associated with adverse effects such as acute lung injury, transfusion-associated circulatory overload, and transfusion-associated graft versus host disease.[28,29]

Anesthesia Considerations

Clinical manifestation of patients with advanced ESLD include encephalopathy, acute kidney injury, and restrictive lung disease because of ascites and pleural effusions. Moreover, difficult venous access with vein thrombosis and the presence of collateral circulation add to the increased risk of infections, and remote, nonsurgical working areas present a real challenge for the anesthetic team.

Although initially most institutions performing TAVR[2] elected for general anesthesia similar to the manner SAVR was approached, nowadays most of these procedures are performed under sedation with the continuous possibility of conversion to general anesthesia due to technical or anesthetic complications.[30]

Sedation of patients with LC and severe valvular heart disease always runs the risk of bronchoaspirative events because of a nonprotected airways in patients with intraabdominal hypertension and delayed gastric emptying. Furthermore, hypoxemia from sedation, decubitus, and a certain degree of pulmonary edema may be accentuated during the procedure and need further interventions, such as use of high-flow nasal oxygenation.

In the case of needing transesophageal echocardiography (TEE), general anesthesia may be required. Recent upper gastrointestinal endoscopy is of great usefulness to study and treat both esophageal varices and portal hypertensive gastropathy to avoid bleeding during TEE, and especially after systemic heparin administration. Varices grade III or banding performed during the last 30 days precludes TEE insertion.

Technology is already with us, and it will continue to evolve in forthcoming years. What society needs are good clinicians from different specialties able to allocate these costly resources to the indicated patients. Probably, all patients with LC and severe valvular heart disease will not need a transcatheter intervention, but more patients will be amenable to liver transplant by successfully treating their heart valve disease.

Conflict of Interest

None.

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