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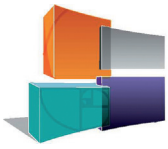

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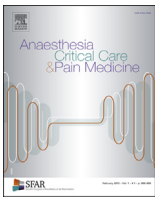

Original Article

New markers for early detection of acute kidney injury after transcatheter aortic valve implantation

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ABSTRACT

Background: Acute kidney injury (AKI) is a frequent complication after a transcatheter aortic valve implantation (TAVI). Biomarkers such as urinary G1 cell cycle arrest proteins (TIMP-2 and IGFBP7) and sonographic evaluation (Doppler Renal Resistive Index [RRI]) have been advocated to predict AKI at an early stage after a TAVI-procedure. The primary aim was to determine the predictive value of these markers to detect AKI after a TAVI-procedure at an early phase.

Patients and methods: In a prospective observational study, 62 consecutive patients were scheduled for a TAVI. AKI was assessed based on the KDIGO criteria. Biomarkers and RRI were measured concomitantly before TAVI, at the first micturition post-implantation and the first micturition on the morning after the procedure.

Results: Twenty-two patients (35%) developed AKI. On the first day after the TAVI-procedure, urinary TIMP-2 and IGFBP7 concentrations increased significantly in patients who developed AKI (0.1, [interquartile] [0.1–0.35] to 0.40 [0.10–1.00] vs. 0.2 [0.1–0.5] to 0.10 [0.10–0.20], $P = 0.012$) with an area under the receiver-operating characteristic curve of 0.71 [0.55–0.83]. Sensitivity was 0.57 and specificity was 0.83 for a cut-off value of 0.35. No significant increases in RRI were found in patients who developed AKI.

Conclusions: Based on the current guidelines for the diagnosis of AKI, the urinary proteins TIMP-2 and IGFBP7 do not detect AKI at an early stage accurately in patients undergoing a TAVI-procedure.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is now considered a valid therapeutic option for patients with severe aortic valve stenosis judged inoperable or considered at a particularly high surgical risk [1]. However, TAVI patients are prone to develop acute kidney injury (AKI) after the procedure [2,3]. AKI has a significant negative impact on patients' prognosis such as the occurrence of myocardial infarction [4], life-threatening bleeding [4] leading to longer hospital stay [5]. AKI could also lead to chronic kidney disease (CKD) [6] and is strongly linked with short and mid-term mortality [4,7], as well as increased healthcare costs [8]. Thereby, detection of renal aggression before renal dysfunction occurs is crucial in TAVI patients because it could guide strategies that might preserve their diminished renal mass and functional reserve [6,9]. Current guidelines recommend the use of Kidney Disease Improving Global Outcomes (KDIGO) criteria for the diagnosis of AKI [10]. These criteria are prolonged low urinary output and serum creatinine (sCr) increment. The former is not an accurate marker of renal injury and is influenced by dehydration, hypovolaemia and anti-diuretic hormone release [11]. A serum creatinine increase is not renal specific and rises only when more than 50% of the functioning renal mass is deteriorated [12]. Therefore, current criteria to identify AKI after TAVI are not accurate enough and belated. Nevertheless, new biologic and sonographic markers of AKI have been shown to rise as soon as renal damage occurs, suggesting promising results. The latest biomarkers tested

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for this purpose are proteins released directly by renal endothelium cells shortly after a kidney aggression [13]. These proteins are the insulin-like growth factor-binding protein 7 (IGFBP7) and the tissue inhibitor of metalloproteinases-2 (TIMP-2) [13]. It has been shown that they could be used to predict AKI after cardiac surgery accurately and earlier than the regular markers [14]. On the other hand, the sonographic marker is the Renal Resistivity Index (RRI). The latter is influenced by the total and local vascular bed compliance [15]. Consequently, cardio renal vascular changes detected with this marker seems to be correlated with initial renal injury [15]. To the best of our knowledge, very few studies have been conducted to determine the role of [TIMP-2] in combination with [IGFBP7] and the Doppler-based RRI detecting AKI before the conventional criteria in patients scheduled to undergo a TAVI-procedure. Hence, the objective of this prospective observational single-centre study conducted in patients undergoing a TAVI-procedure was to assess the predictive value of [TIMP-2] in association with [IGFBP7] and, the RRI as early markers of AKI. The hypothesis of the present trial was that urinary [TIMP-2]*[IGFBP7] and the Doppler-based RRI could contribute in detecting patients developing AKI.

2. Methods

2.1. Patients

This human research, prospective, observational, single-centre trial study was conducted at the Bordeaux University Hospital (Service d'anesthésie-réanimation II, CHU de Bordeaux, France) from September 2016 to February 2017. Ethical approval for this trial (Ethical Committee no. DC 2016/94) was provided by the Ethical Committee of Bordeaux University Hospital, (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France, Chairperson Prof D. Berdaï) on July 11th 2016. Agreement from the Commission nationale de l'informatique et des libertés was also obtained before starting the study (registration number 1984358v0). Data and urine samples were collected according to the present standard practice of care of our institution [16,17]. Therefore, the Ethics Committee declared the present trial not to pertain to article L. 1121-1 of the French public health code and authorised a waiver of the written informed consent. The study was registered on clinicaltrials.gov (NCT02976792). Patients were enrolled in the study if they were 18 years old or older, were scheduled to undergo a TAVI-procedure and gave an explicit consent for the valve implantation. We analysed data from all patients with severe aortic stenosis scheduled to undergo a TAVI excluding those with end-stage CKD, those with intraoperative cardiac arrest and those scheduled for an urgent valve implantation.

2.2. Perioperative patients' care

Prior to implantation, a heart team constituted of interventional cardiologists, cardiac surgeons and cardiac anaesthetists determined the type of valve to implant, the access route and the type of anaesthesia. The femoral approach was the preferred approach and was performed with patients under conscious sedation in addition to local anaesthetic infiltrations. When patients presented severe peripheral vascular diseases of the lower limbs, a transcarotid approach under general anaesthesia was favoured. No special treatment was prescribed to patients with known CKD before the procedure to prevent contrast-induced nephropathy (CIN). Upon arrival in the hybrid operating room, patients were transferred to the operating table. They were monitored with a 2-channel electrocardiogram, pulse oximetry, and bispectral index. One arterial line and two IV lines were inserted in all patients. No indwelling catheter was inserted for the procedure. Patients under conscious sedation received a facial mask for O_2 delivery. This group also received an injection of 30–40 cc of lidocaine 1% at the catheter insertion site and propofol administration using a target-controlled infusion technique for conscious sedation with spontaneous breathing. BIS values were maintained around 65. In contrast, patients under general anaesthesia received a total intravenous anaesthesia-technique using target-controlled infusion models for both remifentanil and propofol. Cisatracurium 0.2 $mg{\cdot}kg^{-1}$ was administered to facilitate endotracheal intubation. After the intubation, lungs were ventilated at normocapnia with a 50% FiO_2. The bio prostheses implanted were either the self-expandable CoreValve valve (Medtronic, Minneapolis, MN) or the balloon-expandable Edwards Sapien XT heart valve system (Edwards Lifesciences, Irvine, CA). Details of the TAVI-procedure have been exhaustively described previously [18]. In both groups, valves were deployed under fluoroscopic guidance only using intravenous contrast injection (Visipaque 270, GE Healthcare Ireland, Cork, Ireland). At the end of the procedure, all patients were transferred to the Coronary Care Unit (CCU) breathing spontaneously. A transurethral catheter was inserted postoperatively only when patients did not empty their bladders within 6 hours after their arrival in CCU.

2.3. Data collection

The preoperative data collected were the following: anthropomorphic data, medical history, patients' drug therapy affecting the kidney function, haematocrit, preoperative left ventricular ejection fraction estimation, logistic EuroSCORE 1 and 2, as well as the preoperative sCr level. The latter was measured in the five days preceding the implantations and was retained as the reference value to determine AKI.

The intraoperative data collected were: the type of TAVI approach, the amount of contrast dye injected, the rate and duration of hypotension defined as mean arterial pressure < 60 mmHg, the amount of fluid administered, the number of patients transfused, the blood-derived products transfused intra- and postoperatively and the duration of the procedure. Upon arrival in CCU, data collected were: the daily urine output and the proportion of patients requiring renal replacement therapy. Serum creatinine level was measured on each postoperative day until its post-procedure peak value was reached or until the 7th postoperative day. The modification of diet in renal disease formula was calculated to estimate the eGFR based on each sCr level measured. Intra- and postoperative significant outcome were recorded according to the standardised VARC-2 criteria [19]. CCU and hospital length of stay, as well as mortality at 30-day were also recorded.

2.3.1. New markers measurements for early detection of acute kidney injury

In all subjects, the RRI measurements and the urine samples withdrawal to measure TIMP-2 and IGFBP7 concentrations were collected prospectively and performed simultaneously before the procedure, at the first micturition post-procedure (or after transurethral catheterisation for patients who did not empty their bladder within 6 hours after their arrival in CCU) and at the first micturition on the morning after the intervention (or 24 hours after their arrival in CCU for patients who had their bladder catheterised).

2.3.1.1. Urine biomarkers – [TIMP-2][IGFBP7].* The urine TIMP-2 and IGFBP7 concentrations were measured using the Nephro-Check® Test (Astute Medical, San Diego, CA, USA). The latter is a fluorescence immunoassay that measures both proteins in

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