Frontiers of valvular heart disease: from aortic stenosis to the tricuspid valve and congenital anomalies

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DOI: https://doi.org/10.1093/eurheartj/ehx083

European Heart Journal (2017) **38**, 611–614
doi:10.1093/eurheartj/ehx083

Frontiers of valvular heart disease: from aortic stenosis to the tricuspid valve and congenital anomalies

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Valvular heart disease has moved from being the Cinderella of cardiology to centre stage in recent years. The development of transcatheter aortic valve implantation or TAVI[1] and its remarkable clinical sucess[2] have stimulated epidemiological[3] and outcomes research, imaging as a modality for the planning of such interventions,[4,5] technological research for new and better tools for such procedures,[6,7] and more recently also the field of antiplatelet agents and antithrombotics. The most recent progress is summarized in a *Current Opinion* '**The year in cardiology 2016: valvular heart disease**', by Ottavio Alfieri and colleagues from the San Raffaele University Hospital in Milan, Italy.[8] The authors note that as expected in this era of rapidly evolving therapeutic modalities and technologies, many scientific contributions are related to the expanded role of percutaneous interventions. New data are now available, consolidating the validity of the transcatheter approach in a variety of subsets of patients and therefore offering new strategies and perspectives in management as outlined in detail in their comprehensive review.

A novel frontier in valvular heart disease is the tricuspid valve, as reviewed by Paul A. Grayburn and colleagues from the Baylor Heart and Vascular Institute in Dallas, Texas in their article '**Tricuspid regurgitation: diagnosis and treatment**'.[9] The authors note that tricuspid regurgitation is the most common lesion of the tricuspid valve, with mild regurgitation being common and usually benign. However, moderate or severe tricuspid regurgitation can lead to irreversible myocardial damage and adverse outcomes. Despite these findings, few patients with significant tricuspid regurgitation undergo surgery. Indeed, the treatment of functional or secondary tricuspid regurgitation remains controversial because of high rates of residual or recurrent tricuspid regurgitation and poor outcomes following surgery. Traditional teaching that functional tricuspid regurgitation resolves on its own if the underlying disease is successfully treated has proven to be incorrect. This review therefore aims to clarify the current management of tricuspid regurgitation by describing the anatomy, pathophysiology, diagnosis, and treatment of tricuspid regurgitation, including the eventual possibility of percutaneous tricuspid valve therapy.

The latter, most innovative aspect is discussed in detail in a second clinical review manuscript entitled '**Percutaneous tricuspid valve therapies: the new frontier**' by Maurizio Taramasso and colleagues from the University Hospital, Zurich, Switzerland.[10] The authors remind us that moderate to severe tricuspid regurgitation affects ~1.6 million patients in the USA, of whom only 8000 undergo tricuspid surgery annually, leaving an extremely large number of patients untreated. Percutaneous procedures are an attractive alternative to surgery for patients deemed to be high-risk surgical candidates. Whereas over the past few years, the development and clinical use of percutaneous approaches such as TAVI, Mitraclip, and mitral valve replacement has increased dramatically, only little progress has been made as regards to the percutaneous treatment of tricuspid regurgitation. In this review, the currently available technologies, among them Mitraclip[11,12] and novel devices,[13,14] which are currently under evaluation, mostly echo-guided,[15] are described in detail and their preliminary clinical results discussed.

As with TAVI, any other percutaneous valve intervention requires careful planning using state-of-the-art imaging modalities, in particular computed tomography (CT). In their clinical research article '**Computed tomography for planning transcatheter tricuspid valve therapy**', Jeroen J. Bax and colleagues from the Leiden University Medical Center in The Netherlands[16] propose a comprehensive anatomical evaluation of the tricuspid valve, right ventricle, and vena cavae, and its spatial relationship with the right coronary artery using CT and investigates the implications for suitability for current technologies as described in the above discussed review by Taramasso *et al.* To evaluate this approach, a total of 250 patients undergoing CT were divided according to the presence of moderate or severe tricuspid regurgitation and less than moderate tricuspid regurgitation. Tricuspid valve annulus, right ventricle, and vena cavae dimensions and the course of the right coronary artery relative to the tricuspid annulus were evaluated. Patients with severe tricuspid regurgitation showed significantly larger dimensions of the tricuspid annulus, right ventricle, and vena cavae. In two-thirds of the patients, the right coronary artery coursed along the tricuspid valve annulus

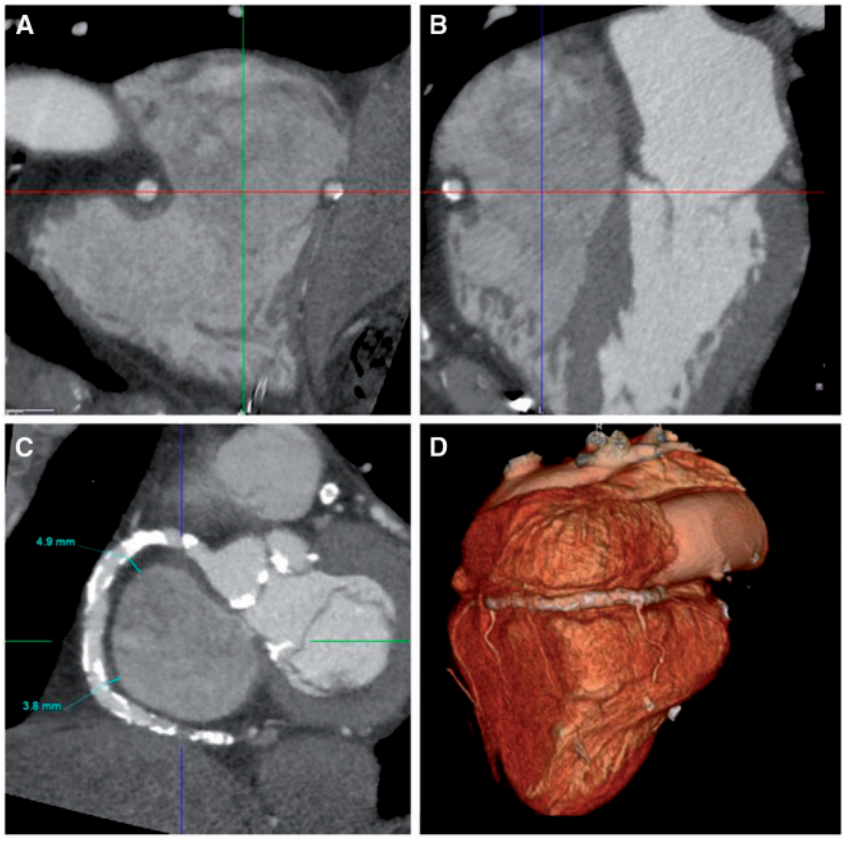

Figure 1 Assessment of the distance between the right coronary artery (RCA) and the tricuspid valve annulus.The long-axis 2- and 4-chamber views (*A* and *B*) were aligned to reconstruct a short-axis view of the tricuspid valve annulus (*C*). At the level of the anterior and posterior tricuspid valve leaflet insertions, the distance to the RCA was assessed. Panel D shows the volume rendered reconstruction demonstrating the course of the RCA completely along the tricuspid valve annulus. (from van Rosendael PJ, Kamperidis V, Kong WKF, van Rosendael AR, van der Kley F, Ajmone Marsan N, Delgado V, Bax JJ. Computed tomography for planning transcatheter tricuspid valve therapy. See pages 665–674.)

(*Figure 1*). Patients with less severe tricuspid regurgitation more frequently showed a course of the right coronary artery superior to the tricuspid annulus at the levels of the anterior and the posterior tricuspid leaflet compared with their counterparts. A less favourable course of the right coronary artery at ≤ 2.0 mm distance from the annulus for current annuloplasty techniques was observed at the level of the anterior tricuspid and posterior leaflets in 13% and 28%, respectively, of patients with severe tricuspid regurgitation. Thus, this is the first systematic approach using CT to define suitability of patients for current transcatheter tricuspid valve devices.

While the most common forms of valvular heart disease affect mainly elderly patients with calcific aortic stenosis as outlined above or functional mitral regurgitation due to heart failure[15,17] or other conditions, congenital anomalies of arterial valves are overall rare, but are common birth defects leading mainly to valvular stenosis. With no pharmaceutical treatment that can prevent disease progression, prosthetic replacement is currently the only treatment choice, incurring considerable morbidity and mortality. Animal models presenting localized anomalies and stenosis of congenital arterial valves like those of humans are important research tools to uncover developmental molecular mechanisms underlying this condition. In a Basic Science article '**Notch–Tnf signalling is required for development and homeostasis of arterial valves**', Bin Zhou and colleagues from the Yeshiva University Albert Einstein College of Medicine in Bronx, New York generated and characterized mouse models with conditionally altered Notch signalling in endothelial or interstitial cells of developing valves.[18] Mice with inactivation of Notch1 signalling in valvular endothelial cells developed congenital anomalies of arterial valves including bicuspid aortic valves and valvular stenosis. Notch1 signalling in valvular endothelial cells was required for repressing proliferation and activating apoptosis of valvular interstitial cells after endocardial to mesenchymal transformation (*Figure 1*). Indeed, the authors showed that Notch signalling regulated tumour necrosis factor α (TNFα) expression *in vivo*, and TNF signalling was necessary for apoptosis of valvular interstitial cells and post-endocardial to mesenchymal transformation development of arterial valves. Further, activation or inhibition of Notch signalling in cultured pig aortic valvular endothelial cells promoted or suppressed apoptosis of valvular interstitial cells, respectively. Thus, the authors conclude that they here for the first time provide animal

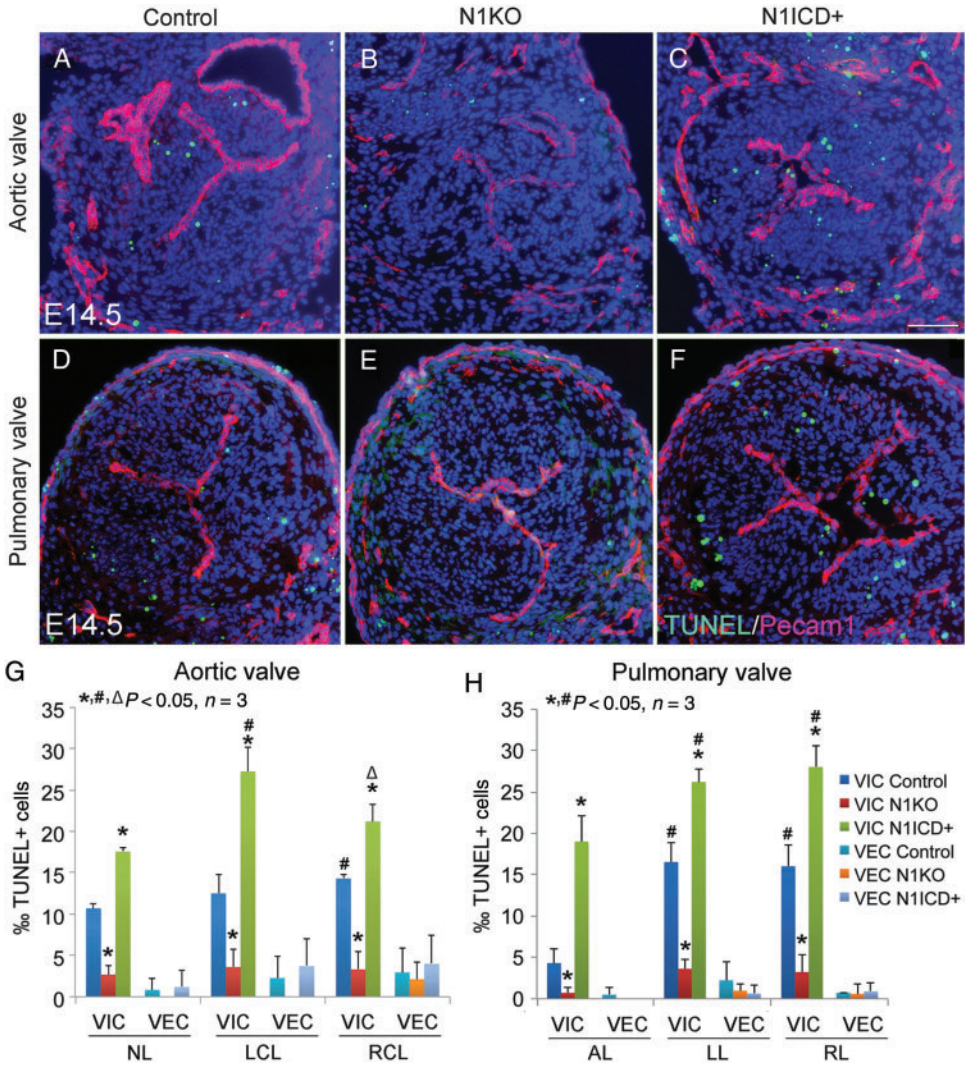

Figure 2 Notch1 in valvular endothelial cells promotes apoptosis of valvar interstitial cells during development of arterial valves. TUNEL assay shows apoptotic cells (green) in arterial valves of E14.5 control (*A* and *D*), N1KO (*B* and *E*), and N1ICD+ embryos (*C* and *F*). Pecam1 staining marks valvar endothelial cells (red). Bar = 50 μm. (*G*) and (*H*) show quantitative results. The data are presented as the ratio of TUNEL+ cells/total valvar endothelial cells or valvar interstitial cells. Statistical comparison was performed using one-way analysis of variance followed by Tukey's test. A P-value of, 0.05 was considered significant. Asterisk indicates comparison with the control in each individual valve leaflet, hash indicates comparison with the non-adjacent leaflet (G) or anterior leaflet (H) in each genotype, and open triangle indicates comparison with the left coronary leaflet (G) in each genotype. (from Wang Y, Wu B, Farrar E, Lui W, Lu P, Zhang D, Alfieri CM, Mao K, Chu M, Yang D, Xu D, Rauchman M, Taylor V, Conway SJ, Yutzey KE, Butcher JT, Zhou B. Notch-Tnf signalling is required for development and homeostasis of arterial valves. See pages 675–686.)

models and show that Notch–TNFα signalling balances proliferation and apoptosis for post-endocardial to mesenchymal transformation development of arterial valves. Their results suggest that mutations in its components may lead to congenital anomaly of aortic valves and valvar stenosis in humans. These provocative findings are further discussed in an interesting **Editorial** by Robert Henry Anderson from Newcastle University in London, UK.[19]

Heart failure is an important complication of valvular, coronary, or hypertensive heart disease. Although huge progress has been made in this condition, as again outlined by the most recent ESC Guidelines,[20] treatment remains essentially palliative in nature. Thus, novel regenerative approaches have been tested with some positive,[21] but mainly neutral results.[22,23] However, cardiopoietic cells, produced through cardiogenic conditioning of patients' mesenchymal stem cells, have shown preliminary efficacy. In a FAST TRACK entitled '**Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double-blind, sham-controlled CHART-1 clinical trial**', Andre Terzic and colleagues for the CHART Program present results of the Congestive Heart Failure Cardiopoietic

Regenerative Therapy trial that aimed to validate cardiopoiesis-based biotherapy in a larger heart failure cohort.[24] This multinational, randomized, double-blind, sham-controlled study was conducted in 39 hospitals. A total of 484 patients with symptomatic ischaemic heart failure on guideline-directed therapy were screened and 348 underwent bone marrow harvest and mesenchymal stem cell expansion. Of those, 315 who achieved >24 million mesenchymal stem cells were randomized to cardiopoietic cells delivered endomyocardially with a retention-enhanced catheter or sham procedure. Of the 271 patients, procedures were performed as randomized in 271. The primary efficacy endpoint was a Finkelstein–Schoenfeld hierarchical composite of all-cause mortality, worsening heart failure, Minnesota Living with Heart Failure Questionnaire score, 6-min walk distance, left ventricular end-systolic volume, and ejection fraction at 39 weeks. The primary outcome was neutral. Exploratory analyses suggested a benefit of cell treatment on the primary composite in the two-thirds of the patients with baseline left ventricular end-diastolic volume 200–370 mL. No difference was observed in serious adverse events. One cardiopoietic cell patient and nine sham patients experienced aborted or sudden cardiac death. Thus, the authors conclude that the primary endpoint was neutral, with safety demonstrated across the cohort. Further evaluation of cardiopoietic cell therapy in patients with elevated end-diastolic volume is warranted. These findings are put into perspective in an **Editorial** authored by Joshua M. Hare from the University of Miami in Florida, USA.[25]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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