observed after coarctation repair is not a new phenomenon, but is simply the continuation of the neurosympathetic process that existed before the coarctation repair.

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 doi:10.1016/j.jtcvs.2007.11.053

Reply to the Editor:

Robicsek outlined in his letter to the Editor in response to our article¹ that arterial hypertension exists distal the coarctation even before coarctation repair. Hypertension in the long-term follow-up is simply the continuation of this neurosympathetic process.

Previously published data from our group² on blood pressure and aortic distensibility in neonates with coarctation before and after surgical repair did not show poststenotic hypertension before repair in general. However, we totally agree with Robicsek and other authors^{3,4} that inborn processes not touched by current modes of repair are also responsible for hypertension in the long-term follow-up after successful repair. We believe that the starting point of the pathophysiologic chain is the inborn alteration of the arterial wall with elastic fiber fragmentation, fibrosis, and cystic medial necrosis, which are later exaggerated by existing hypertension. This causes the increased stiffness most pronounced in the central elastic arteries, the blunted baroreceptor reflex, and the neurosympathetic activation. However, the novelty of our study was the extent of this phenomenon. Our relation to age showed that arterial hypertension has to be expected in almost all patients after coarctation repair in older ages. Close surveillance and aggressive treatment of arterial hypertension might prevent further cardiovascular disease.

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Heart valve tissue engineering: Research should proceed along validated routes

To the Editor:

In their article focusing on in vivo autologous recellularization of a tissue-engineered heart valve, Vincentelli and colleagues¹ raise 2 main questions: (1) Which are the best candidates for scaffold repopulation? (2) Does direct injection of cells into the scaffold guarantee adequate cellular recolonization?

According to the cell type chosen for scaffold seeding, the adoption of nonselected bone marrow-derived mononuclear cells was associated with early degeneration with thickening and retraction of the cusps, growth of fibrotic pannus along the suture lines, and thickening and calcification of the wall conduits. Histologically, a marked inflammatory response with extracellular matrix disarray and macrophage infiltration both in the adventitia and the media layers were observed, along with a loss of the proper collagen allocation between the

ventricularis, spongiosa, and fibrosa of the leaflets. Additionally, a significant increase of both transvalvular and distal gradients were recorded at 4-month follow-up echocardiographic analysis. On the contrary, scaffolds repopulated with mesenchymal stem cells did not evidence either degenerative notes or inflammatory reactions.

These findings might suggest “the onset of a structural deterioration of the scaffold in the [bone marrow–derived mononuclear cell] group and a protective effect of the injections of [mesenchymal stem cells].”¹ We are concerned that such conclusions seem audacious because the study suffers from a main limitation represented by the cell-seeding modality. In fact, the authors, looking for an answer to question number 2, choose to inject the cells directly into the decellularized scaffold (onto the conduit walls and valve annulus, excluding the leaflets), instead of adopting a biomimetic environment.

The adoption of this alternative technique, which has been derived from the myocardial setting,² represents an innovative concept for the valvular field and therefore requires a careful validation. Fluorescent cell tracking, which was performed on 4 of 14 animals in the first postoperative week, evidenced, on day 1, the cell persistence onto the injection site and, on day 7, a few scattered cells into the matrix, the arterial wall, and the leaflets. Moreover, nonlabeled cells of host origin were found.

Is this enough to say that “in situ injection of bone marrow cells into a porcine decellularized scaffold before implantation enhanced the in vivo recolonization and induced full re-endothelialization”?¹ First, endothelialization and scaffold repopulation do not coincide. Even bioprostheses undergo an endothelialization process of the inert components once implanted. Second, the process of repopulation implies an architectural and hierarchic cell-specific distribution along the leaflet’s ventricularis, spongiosa, and fibrosa,³ which was not observed in this experience.

In the article’s “Discussion” section, the authors themselves affirm that they had no direct evidence that cells would grow inside the matrix. According to the hypothesis that injected cells might enhance autologous recellularization, further evidence is needed to draw definite conclusions, and the provided results do not concretely support the initial hypothesis.

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Reply to the Editor:

We thank Drs Di Marco and Gerosa for considering that injection of mesenchymal stem cells (MSCs) in decellularized scaffolds before in vivo implantation represents an innovative concept in the valvular field, and we completely agree that this concept requires a careful validation. However, they expressed some concern about our conclusion that bone marrow-derived mononuclear cell injection induced a structural deterioration of the scaffold and that MSCs induced a protective effect.

We believe that the observation of a deleterious effect of bone marrow-derived mononuclear cells is an interesting point because these cells had never been tested in the field of valve tissue engineering, whereas they are currently used in clinical assays in the field of myocardial failure. Also, we agree that endothelialization and scaffold recolonization are 2 distinct processes that do not always take place together. However, Bertipaglia and colleagues¹ have demonstrated that 2 weeks after in vitro interstitial cell seeding into decellularized leaflets, grafted cells were found penetrating the decellularized scaffold and expressed various immunologic differentiation patterns, such as fibroblasts, myofibroblasts, smooth muscle cells, and

also endothelial cells. Similarly, we observed a significant recolonization after injection of MSCs, and moreover, as stated in our article, pulmonary leaflets exhibited a typical organization in 3 layers (ie, fibrosa, spongiosa, and ventricularis) in each animal of the MSC group.²

Finally, several lines of evidence indicate that in vivo recellularization of valve scaffolds is no longer a “nonvalidated route.” In a previous work we demonstrated evidence of spontaneous recellularization of a decellularized valve.³ Such results were emphasized by Dohmen and coworkers⁴ comparing in vitro seeded and nonseeded valves implanted in sheep. After 6 months, valves from both groups exhibited full recolonization of the leaflets, with comparable hemodynamic behavior and valve remodeling.

We recognize that further studies are needed to compare spontaneous recolonization of an appropriated scaffold and the effects of in situ injection of autologous cells. Also, we have to investigate how injected autologous MSCs improve in situ recolonization by myofibroblasts and endothelial cells or improve host cell migration. However, the challenge seems now to understand and to favor in vivo, rather than in vitro, valve scaffold recolonization.

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Percutaneous aortic valve replacement with the CoreValve bioprosthesis

To the Editor:

We read with interest the recent article by Marcheix and colleagues¹ in the *Journal* dealing with percutaneous aortic valve implantation. They reported their experience using the second generation (21F) of the CoreValve prosthesis (CoreValve, Inc, Paris, France) in 10 consecutive high-risk surgical patients (median logistic EuroSCORE of 32%). The prosthesis was successfully delivered in all cases, with a doubling of the aortic valve area (from 0.57 ± 0.19 to 1.2 ± 0.35 cm²) and a significant decrease in transvalvular gradient.

We would like to comment on these results and also ask for some clarifications regarding their data:

Prosthesis sizing is an important issue. On one hand, undersizing may be responsible for valve migration (owing to poor anchoring), perivalvular leak, or patient-prosthesis mismatch. On the other hand, oversizing may theoretically lead to coronary obstruction or favor atrioventricular block. There is actually only one available size of the CoreValve prosthesis, with a 21-mm bioprosthesis implanted within the stent frame. This valve is at the present time indicated when the aortic annulus diameter ranges from 20 to 27 mm.² Although the authors did not report the annulus size in their group of patients, we do not understand how proper sizing could be achieved with a single-sized bioprosthesis.

Aortic bicuspidy is observed in half of cases of severe aortic stenosis.³ In our experience, misdeployment of a valved stent is likely to occur within a bicuspid aortic valve,^{4,5} which may alter its long-term durability. Did the authors face a case with a bicuspid aortic valve or have they systematically preoperatively screened the patients and excluded for the endovascular procedure those with a bicuspid aortic valve?