validity, and perhaps the relevance of such hemodynamic measurements.

In regard to the effects on diastolic function induced by SVR, he ignores our article published in *Circulation* in 2004,³ in which we demonstrated that SVR induces a mechanical resynchronization through improvement of contraction and relaxation phases leading to early improvement in diastolic function, despite the marked reduction of end-diastolic volume. These data have been confirmed at follow-up in a more recent article.⁴

Diastolic filling depends on several “static and dynamic” variables, and in our opinion it is too simplistic to infer that surgical reduction of end-diastolic volume equates with induction of impaired diastolic function. End-diastolic volume reduction during SVR is the consequence of scar tissue exclusion. Moreover, an increase in stiffness does not necessarily mean a reduction of ventricular filling and worsening of clinical status, given that many dynamic factors can partially compensate for alterations in elastic properties of the ventricular wall. On the other hand, a majority of healthy elderly individuals are free of disease despite the presence of left ventricular diastolic dysfunction as detected by echocardiography. In addition, it is well known that diastolic dysfunction is neither necessary nor sufficient for the development of a heart failure clinical syndrome: Additional complex interactions with metabolic, neurohormonal, and especially renal factors are likely to be required.⁵ At present, we do not think that valid data exist to show that SVR induces changes in diastolic function that are able to turn heart failure with reduced ejection fraction into heart failure with preserved ejection fraction!

With specific regard to our article, Dr Buckberg seems to assume “a priori” that a reduction in SV necessarily implies a worsening of hemodynamics and, parenthetically, cardiovascular equilibrium. In our article, and more precisely in our previous response to

Parachuri, we emphasized that post-SVR SV reduction was not present in all patients but only in those with resting SV higher than normal, whereas in patients with reduced resting SV, SVR induces an increase in SV. We hypothesized that the resting SV higher than normal and proportional to end-diastolic volume increase was due to “congestion” in a vision of backward heart failure mechanism, whereas the increase in SV in patients with resting decreased SV was likely due to ventricular afterload reduction after SVR. The message of our article was that SVR, on the basis of our data, tends to normalize resting SV, and this is not at all in disagreement with postoperative clinical improvement.

We think that one should not interpret hemodynamic changes in a biased way, taking into account mainly or only the direction of changes, but should frame them in a correct pathophysiologic picture considering the setting in which changes begin, the meaning, and the mechanism underlying such changes.

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Reply to the Editor:

We thank Dr Buckberg for his thoughtful comments on our article.¹ We obviously agree that a positive correlation (or a “logical” relationship) between clinical findings (in our case New York Heart Association class, quality-of-life score, and 6-minute walking distance) and hemodynamic measurements is reassuring and supportive for the validity and consistency of the entire data set. The implicit and plausible assumption is that patients would be expected to profit from surgical ventricular restoration (SVR) if this intervention somehow improves their cardiovascular function. However, cardiovascular function has many components, and the relative importance of each component on overall cardiovascular status might depend on factors such as the level of exertion.

Clinical parameters provide a highly valuable overall outcome measure, but a positive clinical response to SVR does not necessarily imply that all components of the underlying cardiovascular function have improved. With regard to SVR, theoretical models predict that the intervention is a “balancing act” between positive effects on systolic function and negative effects on diastolic function.² Our findings support this hypothesis, but we also conclude that based on more global parameters, such as cardiac output and stroke work, and the mentioned clinical parameters, the positive effects (improved systolic function, reduced wall stress, and reduced dyssynchrony) apparently outweighed the negative effects (reduced diastolic function) in our patient group. We believe that this type of detailed analysis of cardiovascular

function is key to understanding the working mechanisms of SVR and explain the somewhat variable reported success.^{3,4} The pathophysiology of the selected patients, the details of the surgical intervention, such as the amount of volume reduction, the applied additional surgical interventions, and the interactions between these factors, all could “tip the balance.” Identification and quantification of the specific effects of SVR on the various components of cardiovascular function ultimately might help to select optimal candidates and potentially to further optimize this intervention to put more weight on the positive side and lift the negative side.

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CARDIAC XENOTRANSPLANTATION TECHNOLOGY PROVIDES MATERIALS FOR IMPROVED BIOPROSTHETIC HEART VALVES

To the Editor:

In their recent article published in the *Journal*, McGregor and colleagues¹

provide further evidence that bioprosthetic heart valves (BHVs) constructed from wild-type (genetically unmodified) porcine or bovine sources are less than optimal, as previously reported and discussed by others.²⁻⁵ Because of the expression of Gal α 1,3Gal (Gal), and possibly other porcine or bovine antigens, they are susceptible to inflammation, calcification, and failure.

The model used by McGregor and colleagues is not ideal. (1) The pig tissue was implanted into the subcutaneous tissue of the recipient, and therefore was not in direct contact with blood (in which anti-pig antibodies circulate). (2) The pig tissue was coated with anti-Gal antibody before implantation, rather than being continually exposed to anti-pig antibodies (which are continually being produced by a human recipient, which is not the case when a Gal-positive animal, eg, rat or rabbit, is used as the recipient of the graft). (3) The pig graft was exposed only to anti-Gal antibodies and not to other human anti-pig (anti-non-Gal) antibodies. Nevertheless, despite these limitations, the authors clearly demonstrate the detrimental effect of using porcine or bovine tissues that are susceptible to human anti-Gal antibodies and make a strong case that tissues from α 1,3-galactosyltransferase gene-knockout (GT-KO) pigs, which do not express Gal, should be the sources of BHVs, as suggested previously.²⁻⁵

As the authors point out, GT-KO mice and pigs, both of which make anti-Gal antibodies (and therefore mimic humans in this respect), are now readily available for future experimental studies. However, despite the reservations the authors express, the pig-to-nonhuman primate model would clearly be the optimal model. Indeed, studies have already clearly shown that GT-KO porcine tissues elicit a weaker inflammatory response than wild-type (unmodified) pig tissues when implanted into nonhuman primates.⁶

However, why limit clinical trials to the use of tissues from GT-KO pigs, when GT-KO pigs that express one or more complement-regulatory proteins (eg, CD46, CD55) are also available? The expression of a complement-regulatory protein would almost certainly protect the tissues further from immune injury, particularly because there will also be a response to non-Gal antigens. Furthermore, pigs are also becoming available that express human anti-inflammatory or antithrombotic transgenes (eg, CD39 or thrombomodulin), which are likely to provide even greater protection. It can realistically be concluded that survival of BHVs from such genetically engineered pigs would be extended significantly.

The biggest hurdle to the use of genetically engineered pigs as sources of BHVs, despite compelling reasons to do so, would seem to be related to business economics. The cost of genetically engineered pigs would be considerably more than the minimal cost of wild-type pigs. As pointed out previously,⁵ if a BHV from a genetically engineered pig functioned in the patient for a significantly longer period of time, this would clearly be in the patient's interests, but it is unlikely to be to the economic advantage of the company supplying the BHV. The cost of the BHV would be significantly greater, and the need for replacement would be significantly reduced.

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