

points. In fact, inertial drop is unaffected by the distance between measurement points when these are sufficiently outside the mitral jet core. In contrast, the convective force plays a role only when the second point is within the jet core; otherwise, its contribution is negligible.

The graph of pressure drop reported in Figure 2 of Firstenberg et al. (1) study and computed between points 5 cm apart can be misleading and of difficult interpretation because it is not linked to a space-time map of pressure. A relevant positive contribution of convection is shown there, which is always between 0.5 and 1 mm Hg during the entire filling period. This means that the velocity in the ventricle, at a distance of 3 cm from the mitral plane, must be always >25 cm/s, even in the diastolic period, which for a normal heart rate and normal flow propagation velocity is not a common finding. In addition, it is also difficult to understand how the total pressure may remain positive during the deceleration phase of the E-wave. In fact, because the inertial contribution is the flow acceleration, during deceleration the pressure increases along the direction of flow; thus, a negative atrium-ventricular pressure difference can be predictable.

From the space-temporal maps, we calculated the pressure difference among three pairs of points at different distances, and the respective results are plotted in Figure 1. As we can see, the convective term disappears when the points are separated by 5 cm (2 cm inside the atrium to 3 cm in the ventricle), a distance similar to the example by Firstenberg et al. (1). In our example, the two points are outside the jet core, and the pressure drop is zero at the maximum of mitral velocity. Figure 1 shows little changes when the two points are closer (1 cm in the atrium and 2 cm in the ventricle). In contrast, an important convective effect appears only when the second point is placed inside the jet (1 cm into the ventricle). In this case, the pressure presents a comparable influence of both terms. However, even in this case, pressure at the E-wave still presents an inversion of sign at the end of the deceleration when inertia is negative and velocity (convection) goes to zero.

In conclusion, we underline how convective and inertial terms of pressure are dependent from the relative position of measurement points. Space allocation of convective and inertial forces by the analysis of the atrioventricular velocity field allows a better interpretation of pressure map in hemodynamic terms.

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digital image processing of color Doppler M-mode maps to noninvasive evaluation of the left ventricular diastolic function: a dedicated software package. *Ultrasound Med Biol* 2000;26:603-11.

REPLY

We appreciate the comments of Tonti et al. regarding our recent publication (1). We agree that transmitral flow is a very complex three-dimensional process that can be approached only as an approximation when the Euler equation is applied to color M-mode images. Nevertheless, previous studies (2) using contrast agents have demonstrated that most of the streamlines of flow follow a unidirectional vector along the long axial dimension of the left ventricle (LV). The validity of this concept is further supported by the accuracy of our results. In fact, we demonstrated that this approach could quite accurately predict the total pressure drop across the normal mitral valve, an impossible task with the simplified Bernoulli equation. Tonti et al. correctly point out that display of pressure differences at just two locations misses the subtlety of the spatiotemporal pressure distribution within the LV inflow tract; our methodology, in fact, provides the full spatiotemporal map from which we extracted pressures at locations corresponding to our multisensor catheter. Tonti et al. state that the convective term should completely cancel out at a 5-cm sensor separation, but this assumes complete pressure recovery across the valve, which may not occur owing to turbulence in the inflow jet and vortices that form at the mitral tips. Indeed, if there were complete pressure recovery, there would be no net pressure drop across even stenotic valves.

The noninvasive calculation of true pressure drop across the normal mitral valve is only one application of quantitative analysis of the color M-mode Doppler image. Even more remarkably, this approach has been shown to be able to quantify the very small (1-4 mm Hg) pressure gradients between the base and apex of the LV that are a manifestation of diastolic suction. This has been validated in a canine model (3), and it was recently used to detect the 1-2-mm Hg increase in diastolic suction that occurs in submaximal exercise (4). Such gradients have been shown to decrease in ischemia (5) and increase with revascularization (6). Thus, digital image processing of color M-mode data may yield new noninvasive quantification of diastolic function that should be widely applicable in the clinical setting.

Although the measurement of the very small pressure gradients is difficult even by (perhaps especially by!) micromanometer catheters, we believe that our data are as accurate as can currently be obtained in patients, and we stand by our analysis as presented. We hope that studies such as ours (1,3,4,6) and by Tonti et al. (7) will stimulate further interest in quantitative color Doppler analysis.

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Paclitaxel-Coated Stent: Is There a Light at the End of the Tunnel?

We read with great interest the study by Drachman et al.(1). Their study determines long-term effects of stent-based paclitaxel delivery and its influence on neointimal thickening in a rabbit injury model.

Their report highlights the importance of stents with drug delivery capabilities and therefore signals the beginning of the era of "smart" stents. An important question unanswered in their study is the gender bias in paclitaxel therapy. It is well established that the chemotherapeutic effect of paclitaxel is mediated through the plasma membrane estrogen receptors (2). It is also widely accepted that this is particularly effective in breast and ovarian neoplasms (3-5).

In contrast, the estrogen receptors in the human cells, including arterial smooth muscle cells (SMC), are probably less developed in the male cell system. Therefore, it will be extremely interesting to investigate the effect of paclitaxel-coated stents on myointimal hyperplasia in male and female animals.

Another issue of this antiproliferative approach for restenosis is the nonselective nature of this modality, which also includes suppression of endothelial cell growth. Although the Drachman et al. (1) study along with others demonstrates complete endothelialization of the coated stents at follow-up, histology is not always an absolute indicator of the endothelialization process. Many believe there is the phenomenon of pseudo-endothelialization. Synthetic or proliferative SMC that line the surface of the vessel after injury may perform many, but not all, functions of endothelial cells. Therefore, functional studies are necessary to address the issue of true endothelialization and, subsequently, late thrombosis.

Finally, the issue of modulation of collagen production by SMC

needs to be addressed. The arrest of SMC migration and proliferation will not be enough to reverse the process of restenosis. It might be that paclitaxel therapy of the vessel wall also abolishes collagen production. Importantly, further in vitro and in vivo studies will help to understand antirestenotic properties of this compound.

Thus, additional experimental studies that will address all these issues might indeed allow us to see the beginning of the end of a long and difficult journey of restenosis prevention.

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REPLY

We very much appreciate the comments of Kipshidze et al. regarding our report on long-term reduction of experimental restenosis using a paclitaxel-releasing stent (1). Their insights underscore the challenges we all face in translating "bench-top" triumphs to techniques that benefit our patients.

It is interesting to consider the role played by the estrogen receptor in smooth muscle cell migration and proliferation (2), and it will be important to determine whether paclitaxel's antirestenotic effects are, at least in part, effected through this receptor system. It is worth noting, however, that paclitaxel's effects are myriad, and that attributing all to plasma membrane estrogen receptors may not be accurate. Such mechanistic insight may extend our understanding of clinical restenosis.

We reiterate concerns that experimental models of endothelial cell function are incomplete and may not always mirror responses in humans. Following experimental arterial injury, the endothelium plays an important role in guiding the healing process, modulating neointimal proliferation, controlling extracellular matrix deposition, regulating vasomotor tone, and protecting against luminal thrombus deposition. Although present laboratory methods allow us to examine the histologic impact of arterial injury on endothelial viability, specific aspects of endothelial cell function are