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Current Status of Flow Convergence for Clinical Applications: Is It a Leaning Tower of "PISA"?

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Spatial appreciation of flow velocities using Doppler color flow mapping has led to quantitative evaluation of the zone of flow convergence proximal to a regurgitant orifice. Based on the theory of conservation of mass, geometric analysis, assuming a series of hemispheric shells of increasing velocity as flow converges on the orifice—the so-called proximal isovelocity surface area (PISA) effect—has yielded methods promising noninvasive measurement of regurgitant flow rate. When combined with conventional Doppler ultrasound to measure orifice velocity, regurgitant orifice area, the major predictor of regurgitation severity, can also be estimated. The high temporal resolution of color M-mode can be used to evaluate dynamic changes in orifice area, as seen in many pathologic conditions, which enhances our appreciation of the pathophysiology of regurgitation. The PISA methodology is potentially applicable to any restrictive orifice and has gained some credibility in the quantitative evaluation of other valve pathology, particularly mitral and tricuspid regurgitation, and in congenital heart disease. Although the current limitations of PISA estimates of regurgitation have tempered its introduction as a valuable clinical tool, considerable efforts in in vitro and clinical research have improved our understanding of the problems and limitations of the PISA methodology and provided a firm platform for continuing research into the accurate quantitative assessment of valve regurgitation and the expanding clinical role of quantitative Doppler color flow mapping.

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Building the Tower

The combination of two-dimensional echocardiography with spectral Doppler ultrasound allowed recognition of the distribution of regurgitant flow in relation to surrounding anatomy (1–3), yet it was only with the introduction of Doppler color flow mapping that a spatial appreciation of intracardiac flow velocity became clinically practicable (4–8). Doppler color flow mapping was initially used for valve regurgitation like an "ultrasound angiogram," which was in fact a naive interpretation of this velocity vector technology. Reasonable success for semiquantitative assessment of severity was initially reported in mitral regurgitation (6,8,9) compared with angiography, when the color flow regurgitant jet distribution was analyzed, but it quickly became clear that the spatial jet distribution was significantly affected by both instrumentation (10) and hemodynamic factors (11). For this reason, the present review mainly concentrates on the role of Doppler color flow mapping to analyze the zone of proximal flow convergence, generally based on the principles of conservation of mass, and alludes to the early work on spectral Doppler and color Doppler of jet flows only by introduction and reference.

Characteristic alterations in flow dynamics that occur *proximal* to a stenotic or regurgitant orifice had long been understood in fluid mechanics (12) but had been largely unrecognized in clinical cardiology until Doppler color flow mapping enabled visualization of spatial flow characteristics in relation to structural detail. Interest in using color flow velocity information quantitatively resulted in early reports of the presence of flow convergence, or spatial acceleration of flow proximal to serial obstructive lesions in vitro (13) and proximal to aortic coarctation in vivo (14). These reports demonstrated that by using computer-enhanced analysis of the color images, it was possible to estimate the rate of spatial acceleration, which contained quantitative information on the severity of obstruction. As an example, in patients with coarctation of the aorta, by measuring how much this flow convergence zone narrowed proximal to the coarctation site, it was possible to infer the severity of the obstruction even if it could not be directly imaged.

The first recognition that flow acceleration existed proximal to a regurgitant orifice was reported by Bargiggia et al. (15) and separately by Okamoto et al. (16), both using color Doppler flow mapping. Okamoto et al. (16) described the presence of a hemispheroidal zone in regurgitant mitral valves, whereas Bargiggia et al. (15) used this information to make quantitative estimates of regurgitant flow rate. Yoshida et al. (17) utilized the presence of flow acceleration of the left ventricular side of the mitral valve in combination with the jet

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direction to evaluate the characteristics of mitral valve prolapse. Appleton et al. (18) further described the presence of proximal flow convergence in mitral regurgitation as an indicator of severity, but the concept that flow convergence could also be evaluated *quantitatively* by Doppler color flow to compute regurgitant flow rate was first fully reported by Recusani et al. (19)* who used the proximal flow convergence zone to assess volume flow in an in vitro model of regurgitation. Although this first study was performed using constant flow and idealized imaging conditions, it formed the basis for all current concepts of regurgitant flow quantitation by flow convergence methods.

The building blocks. The concept that volume flow can be determined from the flow convergence zone proximal to a regurgitant orifice is based on several assumptions: (1) All flow that passes through the flow convergence zone also passes through the regurgitant orifice. Very close to a valve surface, this assumption is usually a valid one because the flow convergence region is constructed from flow velocities accelerating toward and through the regurgitant orifice. (2) There is symmetrical, unconstrained acceleration of flow from all angles into an infinitesimally small, round, single regurgitant orifice, producing a hemispheric geometry of flow. In these circumstances, as flow accelerates toward the regurgitant orifice, the flow convergence zone will comprise isovelocity hemispheric shells of increasing velocity and decreasing surface area closer to the orifice. Each shell will have a particular velocity relative to its surface area that should be constant for any of the hemispheric flow regions. This product of velocity (cm/s) and hemispheric surface area (cm^2) forms the basis of the regurgitant volume flow calculation. If the radius of the isovelocity hemisphere is measured as the distance from the regurgitant orifice, then the surface area can be calculated as follows:

$$\text{Hemispheric surface area} = 2\pi r^2,$$

where r = radius from the regurgitant orifice. If the proximal isovelocity surface area chosen is at a position of color aliasing, then the surface velocity will be known, either as the Nyquist velocity value or a higher velocity multiple of the Nyquist velocity, depending on the number of previous aliases.

In theory, this proximal isovelocity surface area, or PISA, allows an estimation of flow rate through the regurgitant orifice, and as a zone of accelerating, laminar flow imaging this area should be much less dependent on either instrumentation or hemodynamic factors than the spatial jet distribution within the receiving chamber.

State of the Art

Using PISA as a method of quantitating flow is highly attractive, particularly in mitral valve regurgitation, where the direction of the regurgitant jet in the receiving chamber is difficult to predict and where interaction with the chamber wall causes significant alteration in jet characteristics (20–22). Additionally, instrumentation factors, including pulse repetition frequency and color flow gain as well as the driving pressure of regurgitation, all have significant effects on the color Doppler-displayed spatial jet distribution. Because the mitral valve is ideally oriented for echocardiographic and Doppler imaging, it is hardly surprising that the main thrust of investigation has been directed at the quantitative assessment of mitral regurgitation and that interest in PISA calculations has spawned a number of recent in vitro and clinical studies in this area.

Mitral valve regurgitation: experimental modeling and clinical application. Although the concept of using flow convergence to estimate regurgitant volume or regurgitant flow rate appears relatively straightforward, the assumptions in the methods are oversimplifications of the fluid dynamics of valvular disease. In vitro and computational studies play an essential role in understanding the results of Doppler color flow mapping and directing possible clinical applications that can be tested in vivo. Extensive in vitro and clinical investigations have highlighted some of the more important physical constraints of the technique. They have also highlighted the dynamic alterations that occur within the acceleration zone. Both the physical constraints and the dynamic changes have considerable effects on the clinical application of the flow convergence method of estimating the severity of mitral valve regurgitation.

The earliest flow images published showed hemispheric zones of aliasing. However, color Doppler-like pulsed Doppler is angle dependent, and color images are therefore not truly representative of flow velocity vectors. The assumption that the proximal isovelocity surface areas are hemispheric is not always valid. Rodriguez et al. (23) predicted that if the regurgitant orifice was infinitesimally small, then the flow convergence region would be hemispheric right up to the regurgitant orifice. However, with an orifice of finite size, as occurs in the clinical situation, there would be a progressive flattening of the isovelocity surfaces as they approach the regurgitant orifice (23), suggesting that the assumption of a hemispheric flow region would be valid only for distances greater than two orifice diameters from the regurgitant orifice. One would not expect this to be too problematic clinically because it would seem wise to measure an isovelocity hemisphere distant from the orifice so as to minimize potential errors in estimating the radius of the hemisphere. This measurement can be achieved quite simply by altering the color baseline shift, thereby moving the position of color aliasing farther from the regurgitant orifice (24). However, using a low velocity alias that is too distant from the regurgitant orifice will cause a potential overestimation of the true flow rate, as a function of mapping a flow convergence region where isovelocities are *hemispheroidal* rather than hemispheric at this point (25,26), an observation that was also confirmed by initial reports of flow velocity mapping using magnetic resonance imaging (27,28). The concept of the developing proximal flow

*Recusani was from Pavia, Italy and used the term "flow convergence." Although the subsequent acronym "PISA," or proximal isovelocity surface area, was later used, Pisa was not the city of origin of this work.

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field is important in understanding the limitations of PISA methods. Data suggest that the proximal flow field alters from essentially laminar flow in the body of the ventricle, to a hemispheroidal flow as lateral forces entrain it toward the orifice, to a truly hemispheric flow field and finally a progressively flattening field near the orifice. The position chosen for PISA estimation is critical for accurate quantitative evaluation. In addition, if measured at too great a distance from the orifice entrance, there is a potential contribution of flow destined for other places, like the aorta, contaminating the flow field. Similarly, Zhang et al. (29) showed that in an animal model of mitral regurgitation, an overestimation of flow rate occurred if they used the first alias velocity is used where the flow field is more hemispheroidal, and a significant underestimation of flow rate occurred at the third alias in a flattened flow field near the orifice. In their study, the use of the second alias velocity was more predictive of the actual regurgitant flow rate. Deng et al. (26) utilized computer-enhanced analysis of Doppler color flow map images to define the relation of velocity thresholds to regurgitant pressure gradient over a range of orifice sizes. For a given shape of isovelocity surface area, it appears possible to select a velocity threshold based on regurgitant pressure gradient that will provide accurate quantitative analysis of volume flow irrespective of orifice size. For pulsatile flows, this might mean that the velocity threshold that should be used for best accuracy might change as a function of the pressure decrease during systole.

The accuracy of the proximal isovelocity surface area to estimate volume flow is highly dependent on radius measurement from the regurgitant orifice and definition of the orifice point of origin. This potential error can be minimized by using high resolution imaging with zoom magnification, but the exact position of the regurgitant orifice may still be difficult to define. Even in severe mitral regurgitation, the zone of proximal flow convergence is relatively small, and measurement errors will have a significant impact on the estimated regurgitant flow rate. Vandervoort et al. (30) proposed a novel automated algorithm that would estimate the position of the regurgitant orifice relative to the flow field as imaged by Doppler color flow mapping. Their method suggests that in a region of flow convergence at a distance from the regurgitant orifice (usually greater than two orifice diameters, as previously indicated), it is possible to generate an "expected flow field" from the regurgitant orifice by computer simulation. Because the true location of the orifice is not known, multiple expected flow fields can be derived and compared with the observed flow field imaged by Doppler color flow mapping. In this way, the derived flow field that most closely matches the observed flow field will pinpoint the location of the regurgitant orifice, which can then be used to estimate regurgitant flow rate from the proximal isovelocity surface area method applied in the conventional manner. One limitation of their particular methodology is that it always assumed a hemispheric flow field for PISA calculation.

In the clinical situation, both time during systole and motion of the valve play a significant role. The mitral orifice is not static throughout systole and it is reasonable to expect that dynamic changes in the regurgitant orifice location may cause substantial alterations in the characteristics of the proximal flow convergence zone. Cape et al. (31) have highlighted the fact that cardiac motion, particularly movement of the regurgitant orifice, may affect the calculation of flow rate using the proximal isovelocity surface area. The transducer will measure the actual velocity relative to the transducer, but this velocity will relate less to the orifice, which may be moving away from the transducer. The result could either overestimate or underestimate the regurgitant flow rate, depending on the relative motion of the orifice. If M-mode echocardiography is used to determine the orifice motion, the velocities of the proximal isovelocity field area may be corrected accordingly.

The maximal flow convergence radius at any velocity value will tend to occur at peak systole where analysis of the proximal isovelocity surface area will result in a value for peak regurgitant flow *rate* rather than the actual regurgitant volume. The temporal sequence of pulsatile flow will vary during systole. Regurgitant flow *volume* will be an integral of flow rates during systole, and if the proximal flow convergence region is to be used to calculate regurgitant flow volume, this must be taken into account. The real-time two-dimensional spatial appreciation of flow velocity by Doppler color flow mapping is only possible with the limited temporal resolution limiting frame rate as a function of the increased requirements in sequential packet pulse trains required for velocity accuracy. This limits the ability of the technique to track the systolic variation in the flow convergence region as a function of changing flow rate. M-mode echocardiography has substantially better temporal resolution and velocity accuracy and has the potential to more readily reflect the temporal effects of pulsatile flow on the flow convergence zone and has become important in pulsatile flow in vitro and in vivo and clinical studies.

The first clinical description of the flow convergence region for Doppler color flow mapping was in the appreciation of the sites of prolapse regurgitation (17) or mitral prosthetic valve regurgitation (32). In a mechanical mitral valve prosthesis it may be difficult to image the regurgitant jet by transthoracic echocardiographic Doppler study because of acoustic shadowing in the left atrium. The presence of flow convergence on the left ventricular side of the mitral valve prosthesis not only confirms the presence of regurgitation, but also localizes the site of the leak with a high degree of accuracy. Although this qualitative appreciation of mitral regurgitation can be clinically useful, it is the potential for more quantitative information that has prompted the evaluation of the flow convergence region in the clinical setting.

An early clinical series with quantitative application of the flow convergence methodology was also described by Bargiggia et al. (33), wherein maximal flow convergence estimates of maximal regurgitant flow rate were compared with the angiographic severity of regurgitation in 52 consecutive patients with mitral regurgitation. That PISA estimates of regurgitation correlated well with angiography ($r = 0.91$) was not only encouraging but was enhanced by the fact that this was

significantly better than the correlation with spatial jet variables in the same patient group (r = 0.75). Since then, similarly encouraging reports (34) have been published comparing flow convergence estimates of regurgitation with the regurgitant flow rate and stroke volume estimated by more conventional two-dimensional echocardiography and spectral Doppler techniques. By combining PISA information with continuous wave Doppler recordings of mitral regurgitation velocity for timing and velocity time integrals, Geisler et al. (35) were able to make an estimate of regurgitant stroke volume and compare this with the invasive assessment of regurgitation severity and angiographic/Fick estimates of regurgitant stroke volume. The flow convergence estimates of regurgitation severity correlated well with angiographic grade of regurgitation (r = 0.91), and there was a similarly good correlation of regurgitant stroke volume estimates (r = 0.88).

The complexities of estimating true regurgitant volume, taking into account the temporal changes in regurgitation through the cardiac cycle or using estimates derived from time velocity integrals, have led to interest in a more basic determinant that can be derived from this method—the assessment of *effective regurgitant orifice area* (36). The effective regurgitant orifice area is smaller than the anatomic orifice area and is sited slightly distal to the anatomic orifice, toward the receiving chamber at the vena contracta of the transorifice flow, but more readily represents the area of regurgitant flow. Because the effective orifice area is a major determinant of the severity of mitral regurgitation, estimation of this variable has particular clinical significance:

$$\text{Regurgitant orifice area (cm}^2\text{)} = \frac{\text{Regurgitant flow rate (cm}^3\text{/s)}}{\text{Regurgitant velocity (cm/s)}}.$$

The proximal isovelocity surface area will generally provide an estimate of the peak regurgitant flow rate if the maximal flow convergence region is utilized, and the peak velocity of regurgitation can be measured directly by continuous wave Doppler. This principle has been tested in vitro to establish that regurgitant orifice area can be estimated, with excellent results (36) (r = 0.99 compared with true regurgitant orifice area). Confirmation of this concept using spectral Doppler echocardiography has also been reported (37). Enriquez-Sarano et al. (36) have also provided encouraging initial clinical results compared with two-dimensional echocardiographic spectral Doppler-derived stroke volume and regurgitant fraction, as well as good angiographic correlation in a subgroup of 20 patients (r = 0.81).

Application of this methodology has been reported in a large unselected patient population with mitral regurgitation to estimate the averaged effective mitral regurgitant orifice area by the proximal isovelocity surface area method (38). This study is particularly welcome as it covers a wide range of regurgitation severity, a wide spectrum of valve morphology. The authors have demonstrated the validity of PISA derived regurgitant orifice area estimates over a broad spectrum of clinical circumstances. It is encouraging to note that it was feasible to estimate effective orifice area in 98% of the study population, and optimal flow convergence visualization was obtained in 92%. There was a tendency to overestimate orifice area for the whole group though not for those patients with optimal imaging characteristics.

Dynamic nature of the regurgitant orifice. The regurgitant orifice is not necessarily constant throughout systole, and this can potentially have a profound effect on the estimation of regurgitant severity. Instantaneous regurgitant orifice area can be estimated from the instantaneous regurgitant flow rate calculated using a PISA methodology based on color M-mode and combined with the instantaneous regurgitant orifice velocity measured using continuous wave Doppler ultrasound. Application of this methodology in clinical studies has yielded interesting insights (39). It would appear that in patients with dilated cardiomyopathy, the regurgitant orifice decreases during systole, whereas in mitral valve prolapse the orifice area increases considerably in midsystole. Regurgitant orifice area probably remains fairly constant throughout systole in patients with rheumatic mitral regurgitation. Color flow mapping combined with conventional Doppler ultrasound may well provide useful clinical information about the pathophysiology of valve regurgitation as well as quantifying its severity. The realization that this dynamic variation in regurgitant orifice area may be dependent on valve morphology was further illustrated by the clinical study of Enriquez-Sarano et al. (38), where overestimation of orifice area was found mainly in the group with mitral valve prolapse, whose regurgitant orifice is larger at end-systole. The PISA estimates of regurgitant flow rely on the "maximal" flow rate, which will tend to overestimate the true mean flow rates, especially in situations of dynamic orifice alteration. Accurate estimation of effective regurgitant orifice area would appear to be possible in the vast majority of patients in whom optimal imaging of the flow convergence region is obtained despite variation in valve morphology.

Other applications. To date there has been limited application of Doppler color flow mapping in the proximal flow zone to other valve pathology. It has been applied to mitral valve stenosis (40), more as a model for validating the flow convergence technique in the clinical setting, although it does provide an additional method of estimating the effective orifice area in mitral stenosis. These studies on mitral stenosis (40,41) were the first to use alterations of the surface of the hemisphere over which acceleration is manifest as a function of inlet geometry and flow constraint. We previously demonstrated (42) that a zone of proximal flow convergence proximal is present in both tricuspid and pulmonary regurgitation. More recently, PISA methodology has been used to quantify the severity of tricuspid regurgitation (43), estimate the tricuspid regurgitant orifice area (44) and define the dynamic changes in the tricuspid regurgitant orifice (45) similar to that for mitral regurgitation, as previously described. As yet, there is scant information with regard to aortic regurgitation, although the fundamental concept of estimating aortic regurgitant orifice area has been established from invasive (46) and noninvasive (47) investigations using conventional spectral Doppler ultrasound.

In studies of congenital heart disease, the flow convergence methodology had been used for flow across ventricular septal defects (48) by transthoracic echocardiography and for atrial septal defects (49) imaged by transesophageal echocardiography. In the former study, both the area of flow convergence on the left ventricular side of the defect and use of the PISA isovelocity methodology to estimate flow across the defect correlated with the shunt flow at cardiac catheterization. In defects that may be difficult to size in certain patients by two-dimensional echocardiography alone, Doppler color flow mapping enhances imaging of the size of the ventricular septal defect and also allows more quantitative information to be obtained from the flow convergence region. The use of transesophageal imaging in patients with atrial septal defects is a further application of the flow convergence technology but possibly of considerably less clinical relevance, as has been stated in a previous comment (50).

The Leaning Tower of PISA: Will It Stand or Will It Fall?

There has been considerable and justifiable interest in the flow convergence zone imaged by Doppler color flow mapping in the past few years, mainly in the hope that it will finally provide an accurate, quantitative estimation of the severity of mitral regurgitation, possibly the most elusive calculation for modern cardiac imaging. As an accelerating flow field, it is hydrodynamically more stable, with laminar flow that is inherently more suited to quantitation by color Doppler than the decelerating jet spray of turbulent regurgitation flow within the left atrium. Nor is the method limited by receiving chamber effects or dependent to the same extent on instrumentation factors or hemodynamic variables. Nonetheless, deriving quantitative information using the proximal isovelocity surface area method has problems and pitfalls highlighted by the extensive in vitro and clinical work previously described. The assumptions used in the analysis of the flow convergence region are based on a nonviscous fluid regurgitating through an infinitely small orifice. A truly hemispheric flow zone is present only at a certain distance from the regurgitant orifice, the so-called sweet zone at a radial distance of greater than one orifice diameter. A hemispheric flow field will occur at a greater distance from a large versus a small regurgitant orifice. The predictability of the hemispheric or the hemielliptic contour methods will also be significantly affected by the inlet geometry, particularly by alterations in the leaflet angle, similar to mitral valve stenosis, where inlet-angle correction of velocity information may be required. That dynamic alteration in orifice diameter complicates the clinical application of PISA methodology, and the temporal effect on regurgitant flow needs to be taken into account if true regurgitant volume is to be accurately estimated, also the position of the regurgitant orifice necessary for radius measurement may change during the cardiac cycle. These limitations reflect the reasons why the PISA tower continues to lean, and an awareness of these pitfalls combined with continuing research are needed to straighten the tower and prevent its downfall. Solutions to some of these problems may already be in sight with automated characterization of the velocity sequences in the acceleration flow field and prediction of the location of the regurgitant orifice using as a primary source digitally coded velocity vector information rather than color images from videotape (51). Estimation of the effective regurgitant orifice area, the major determinant of the severity of regurgitation, appears not only possible, but could be an increasingly practical tool for assessing regurgitation in a large, unselected patient population.

Clinicians may question the need to have accurate estimates of the severity of mitral regurgitation. They may argue that it is not the volume of regurgitation that is important, more its functional consequences, and that this can only be fully judged by symptomatology, clinical examination and the composite result of multiple, often serial investigations. However, as intervention for mitral regurgitation becomes an option at an earlier stage in its natural history with advances in reconstructive surgery and for more rationally judging the effects of pharmacologic treatment, there is a continuing need for accurate evaluation of volumetric mitral regurgitation. There is considerable promise that PISA estimates from Doppler color flow mapping will fulfill this role. Continued clinical and experimental evaluation of both two- and three-dimensional implementations, combined with digital integration of the various aspects of the methodology directly into commercially available ultrasound equipment, should promote enhanced and expanded applications of these methods in clinical cardiology.

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