EDITORIAL

Use of Perfusion Agents to Measure Cardiac Output

Cardiac output (CO) is recognized as one of the most important parameters describing the clinical status of cardiac patients. Maintaining adequate CO is essential to supporting life because otherwise sufficient nutrients will not be available for sustaining tissue metabolism. A drop from normal resting CO of one third has long been considered a level below which further reductions are life threatening (*1*). For most cardiologists, CO represents only systemic output. However, in the article in this issue of *The Journal of Nuclear Medicine* by Taki et al. (*2*), which describes a method for noninvasive determination of CO with ^{99m}Tc-tetrofosmin, a distinction is made specifically for forward CO to account for that percentage of cardiac stroke volume regurgitating backward because of valvular disorders. In cases of valvular disease, forward CO is less than stroke volume times heart rate, and the regurgitant fraction is nonzero.

Scintillation cameras have been used extensively for first-pass imaging not only to compare forward CO (*3*) but also to determine ejection fraction (EF) (*4*). First-pass techniques also have yielded stroke volume ratios for quantification of cardiac shunts (*5*). Although direct regurgitant fraction measurements are possible with radionuclide angiography (*6*), scintigraphy has played a more central role in predicting prognoses for patients with valvular disorders based on measurements of ventricular size, performance and function (*7*). Equilibrium studies supplanted first-pass measurements for EF determination in the 1970s (*8*), and these in turn were replaced largely by EF measurements derived from gated perfusion SPECT data in the 1990s (*9–11*). These developments left determination of CO by the wayside. The ability of gated SPECT methods to compute CO accurately has been disappointing. Stroke volumes have a relatively poor correlation with thermodilution measurements (*12*). Gated SPECT end-diastolic (ED) and end-systolic volume correlations with those of other modalities have been more encouraging, with linear regression coefficients ranging from 0.87 to 0.94 (*12–14*).

The article by Taki et al. rejuvenates the ability of data acquired for SPECT perfusion imaging to provide forward CO and EF. With the declining use of first-pass scintigraphy, there has been no readily available noninvasive means of obtaining CO. The method presented by Taki et al. uses radionuclide time-activity curves obtainable with any ^{99m}Tc agent used for subsequent myocardial perfusion imaging. The technique uses first-pass imaging at 1 frame/s of transit of the bolus through the left ventricle, from which maximum and time-integrated counts are obtained. The left ventricular (LV) time-averaged volume is estimated in this implementation using the Dodge-Sandler single-plane area-length approximation. This method does not require acquisition of gated data. Because images are obtained in the anterior projection, geometric corrections are applied to estimate what volume values would have been obtained had data been collected instead in the true vertical long-axis orientation.

A number of assumptions are involved in this method that are reasonable for healthy subjects. These include the supposition that average camera sensitivity during the LV phase of first-pass transit equals sensitivity during the superior vena cava phase. Using older cameras or studying unusually small patients may involve dead-time complications (*15*). Also, it is assumed that average attenuation factors over the whole thorax equal those over the left ventricle. This may not be the case for some patients, such as females with unusually dense breast tissue for whom artifacts associated with regional attenuation differences are problematic (*16*). It is further assumed that volumes estimated from time-averaged images are the same as true ED volumes. For patients with vigorously contracting hearts, time-averaged count distributions may be shifted toward being concentrated into end-systolic volumes. Also, the Dodge-Sandler volume approximation may be more reliable for patients with normal function and more nearly symmetric left ventricles than for those with severely ischemic myocardial areas and aneurysms. Related to this, the application of geometric corrections to anterior LV dimensions to estimate volumes, which would have been computed from true vertical long-axis views, presumes prolate spheroid shapes.

For these reasons, validation of this new technique would be worthwhile for broader classes of patients than were studied. The most important extension will be for patients with valvular disease with substantial regurgitant fractions. This is a class of patients for whom the observation of larger LV volumes corresponding to lower EFs (*17*) can be expected to break down. Other specific patient groups for whom the accuracy of CO measured by this technique needs to be verified are those with large LV volumes and those with low EFs. This is particularly important for patients with abnormally low CO who have not yet been studied by this new method. In addition, the effect of arrhythmias during the collection of data can markedly affect measured CO and needs to be closely monitored. Finally, the data of this study were collected using tetrofosmin. Although other ^{99m}Tc-based perfusion agents may

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provide CO estimates that are similar to those obtained with the proposed methodology, it is possible that tracer kinetics and extraction fraction differences could produce different measurements; therefore, correlative studies will be important. The verification of this nuclear technique against another nuclear procedure should be extended to include correlations with other methods for computing CO, such as thermodilution and MRI. These validations would be helpful for calibrating CO measurements from this technique with more established methods.

To perform high-quality first-pass studies for any purpose, several precautions must be observed. These include testing that neither bolus transit time nor lung transit time is overly long, thereby compromising the assumptions underlying the use of tracer curves (*18*). Arrhythmias also are of concern, and their prevalence and implications relating to physiologic measurements from gated perfusion SPECT have recently been addressed (*19*). Taki et al. are correct in stating that their method is not as vulnerable to arrhythmias as gated techniques, but measurements made during transient arrhythmias may not represent a patient's usual CO. No method is immune to error in patients with markedly irregular rhythms. Finally, the precision of the method needs to be studied more extensively because of the necessity of manually drawing regions to encompass the time-averaged LV volume. Automation of these techniques and the use of automatic gated SPECT ED volumes (*10,11,20*) could prove helpful to minimize interobserver disagreements.

CONCLUSION

This is an important new method that has potential in evaluating patients with cardiac disease. However, further study is warranted in specific patient populations with validation against other non-nuclear techniques to assess the accuracy and precision of the method for patients with valvular disease and for any cardiac disease for which CO is low. The approach described, if further validated, adds to the armamentarium of nuclear cardiology to provide noninvasive measurement of CO.

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REFERENCES

1. Grossman W. Blood flow measurement: the cardiac output. In: Grossman W, ed. *Cardiac Catheterization and Angiography*. 2nd ed. Philadelphia, PA: Lea and Febiger; 1980:89–93.
2. Taki J, Muramori A, Kinuya S, et al. Forward cardiac output measurement with first-pass technique using ^{99m}Tc-labeled myocardial perfusion imaging agents. *J Nucl Med*. 1999;40:1874–1881.
3. Minssart P, Chatal JF, Grolleau JY, Guihanrd R, Agnely J, Vernejoul P. A correlative study of the measurement of human cardiac output as determined by thermodilution and radiocardiography. *Eur J Nucl Med*. 1978;3:147–152.
4. Schelbert HR, Verba JW, Johnson AD, et al. Nontraumatic determination of left ventricular ejection fraction by radionuclide angiography. *Circulation*. 1975;51:902–909.
5. Gelfand MJ, Hannon DW. Left-to-right shunts. In: Gelfand MJ, Thomas SR, eds. *Effective Use of Computers in Nuclear Medicine*. New York, NY: McGraw-Hill Book Co., 1988:271–287.
6. Janowitz WR, Fester A. Quantitation of left ventricular regurgitant fraction by first pass radionuclide angiocardiography. *Am J Cardiol*. 1982;49:85–92.
7. Rogers WJ, Papapietro SE, Wackers FJT, et al. Variables predictive of good functional outcome following thrombolytic therapy in the Thrombolysis in Myocardial Infarction Phase II (TIMI II) pilot study. *Am J Cardiol*. 1989;63:503–512.
8. Bacharach SL, Green MV, Borer JS, et al. A real-time system for multi-image gated cardiac studies. *J Nucl Med*. 1977;18:79–84.
9. DePuey EG, Nichols K, Dobrinsky C. Left ventricular ejection fraction assessed from gated technetium-99m-sestamibi SPECT. *J Nucl Med*. 1993;34:1871–1876.
10. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med*. 1995;36:2138–2147.
11. Faber T, Cooke C, Folks R, et al. Left ventricular function and perfusion from gated SPECT perfusion images: an integrated method. *J Nucl Med*. 1999;40:650–659.
12. Iskandrian A, Germano G, VanDecker W, et al. Validation of left ventricular volume measurements by gated SPECT Tc-99m sestamibi imaging. *J Nucl Cardiol*. 1998;5:574–578.
13. Mochizuki T, Murase K, Tanake H, et al. Assessment of left ventricular volume utilizing ECG-gated SPECT with technetium-99m-MIBI and technetium-99m-tetrofosmin. *J Nucl Med*. 1997;38:53–57.
14. Nichols K, Tamis J, DePuey EG, Mieres J, Malhotra S, Rozanski. Relationship of gated SPECT ventricular functional parameters to angiographic measurements. *J Nucl Cardiol*. 1998;5:295–303.
15. Adams R, Hine GJ, Zimmerman CD. Deadtime measurements in scintillation cameras under scatter condition simulating quantitative cardiology. *J Nucl Med*. 1978;19:538–544.
16. DePuey EG. Artifacts in SPECT myocardial imaging. In: DePuey EG, Berman DS, Garcia EV, eds. *Cardiac SPECT Imaging*. New York, NY: Raven Press, 1995:169–200.
17. Germano G, Kavanaugh P, Kavanaugh J, Wishner S, Berman D, Kavanaugh G. Repeatability of automatic left ventricular cavity volume measurements from myocardial perfusion SPECT. *J Nucl Cardiol*. 1998;5:477–483.
18. Nichols K, DePuey EG, Rozanski A. First pass radionuclide angiocardiography using single-crystal gamma cameras. *J Nucl Cardiol*. 1997;4:61–73.
19. Nichols K, Dorbala S, DePuey EG, Yao SS, Sharma A, Rozanski A. Influence of arrhythmias on gated SPECT myocardial perfusion and function quantification. *J Nucl Med*. 1999;40:924–934.
20. Nichols K, Depuey EG, Rozanski A. Automation of gated tomographic left ventricular ejection fraction. *J Nucl Cardiol*. 1996;3:475–482.