Evaluation of Myocardial Performance Index to Predict Mild Rejection in Cardiac Transplantation

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Summary

Background: Early diagnosis of heart transplant rejection is mandatory, since even mild rejection can rapidly progress to more severe rejection. Noninvasive diagnosis of heart transplant rejection still remains a challenge.

Hypothesis: The purpose of the study was to determine a possible association between myocardial performance index (MPI) and biopsy score of the heart transplant.

Methods: This is a retrospective cohort analysis of 99 complete Doppler echocardiographic studies from 24 consecutive patients (23 men) performed within 24 h of endomyocardial biopsy. Mean age of the cohort was 50 ± 9 years and mean time from transplantation was 19 ± 21 months (1–81). All patients were in sinus rhythm. Myocardial performance index was calculated as the ratio of isovolumic contraction time plus isovolumic relaxation time divided by ejection time. Left ventricular dimensions, left ventricular mass, ejection fraction, and a number of Doppler indices (E-point velocity, A-point velocity, deceleration time, and deceleration slope) were also measured. The International Society for Heart and Lung Transplantation (ISHLT) grading system was used for the classification of endomyocardial biopsies.

Results: Myocardial performance index was significantly prolonged (0.60 ± 0.13 , 0.68 ± 0.08 , 0.75 ± 0.20 , in biopsy scores 0, IA, and IB, respectively; $p < 0.001$). Isovolumic contraction time was significantly prolonged; isovolumic relax-

ation time was not significantly changed. Ejection time and deceleration time were significantly shortened. Multivariate stepwise regression analysis revealed that MPI and deceleration time were the only independent predictors of biopsy score ($r = 0.48$, $F = 10.53$, $p < 0.0001$).

Conclusion: Myocardial performance index seems to be a useful adjunct in the follow-up of cardiac transplant patients. These preliminary data suggest that a larger study may be indicated to clarify the relevance of myocardial performance index.

Key words: myocardial performance index, allograft rejection, heart transplantation, echocardiography

Introduction

Cardiac transplantation is associated with an acceptable quality of life in patients with end-stage heart failure.^{1,2} In many transplantation centers, the 1-year patient survival rate approaches 85%, the 5-year survival rate is 75–80%, and 50% survival is estimated between 9 and 11 years.^{1,3} Despite improved immunosuppression, acute rejection still remains one of the major causes of morbidity and death. Endomyocardial biopsy is the standard of reference for the detection of graft rejection and the assessment of the adequacy of antirejection treatment. It is an invasive procedure that may present a small risk to the patient and may not always be available; it is also expensive and can be an inconvenience to patients. Furthermore, biopsies at regular intervals for routine late rejection surveillance may delay diagnosis. On the other hand, Doppler measurements of global function may be more sensitive than endomyocardial biopsy if the rejection is patchy or if other types of rejection such as humoral rejection are considered.⁴ Thus, it becomes increasingly important to search for a new, accurate, reproducible, and sensitive technique for detecting cardiac rejection.

Myocardial performance index (MPI) is a new Doppler-derived index that reflects both the systolic and diastolic function of the heart.⁵ It has already been successfully applied to a variety of diseases such as amyloidosis,⁶ dilated cardiomyopa-

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thy,^{7, 8} primary pulmonary hypertension,⁹ congenital diseases,¹⁰ or myocardial infarction.¹¹

During episodes of cardiac rejection, left ventricular (LV) dysfunction is primarily diastolic. Systolic function is usually well preserved during early rejection.^{12, 13} The purpose of this study was to examine a possible association between MPI and endomyocardial biopsy score in patients with episodes of mild rejection. Moreover, the study aimed at evaluating whether the assessment of this index would reduce the frequency of endomyocardial biopsies or guide their timing and allow for a more frequent reliable monitoring of cardiac transplant patients.

Materials and Methods

Study Population

A combined retrospective cohort analysis and prospective study was performed on cardiac transplant patients. Ninety-nine echocardiograms were included, obtained from 24 consecutive patients (Table I). All patients were in sinus rhythm. Patients who were not in sinus rhythm and those with pacemakers, bundle-branch block, or high-grade atrioventricular block were excluded. Mean heart rate was 89 ± 12 beats/min (range 60–122). All patients were on antihypertensive regimen based on diltiazem, enalapril, and metoprolol. They were all normotensive, and a yearly evaluation with 24-h ambulatory blood pressure monitoring was performed. Mean systolic pressure was 123 ± 16.2 mmHg and mean diastolic pressure was 80.2 ± 8.9 mmHg. At the time of the study, all patients were on cyclosporine and azathioprine, and a minority was

taking prednisone because of episodes of refractory rejection in the past.

Parallel to endomyocardial biopsy, a complete M-mode, two-dimensional, and color flow Doppler echocardiographic examination was performed in each patient. Studies were performed using the commercially available Hewlett-Packard machine (Sonos 1000, Hewlett Packard, Andover, Mass., USA) and a 2.5 MHz phased-array transducer. Echocardiographic-pulsed Doppler data were recorded at a sweep speed of 50 or 100 mm/s by a Panasonic AG-7350 videocassette recorder (Model AG-MD830E, Panasonic, Osaka, Japan) and stored on high-quality super VHS videotape for later playback and blinded analysis.

Echocardiographic examination was undertaken using standard views and techniques according to the guidelines of the American Society of Echocardiography.^{14, 15}

*Myocardial performance index*⁵ is defined as the summation of isovolumic contraction time and isovolumic relaxation time divided by ejection time. In the present study, MPI was calculated as follows (Fig. 1): From the mitral inflow Doppler tracings, the time interval "a" from the cessation to onset of mitral inflow and time interval "c" between the R wave of the electrocardiogram (ECG) and the onset of mitral inflow were measured. From LV outflow tracings, the time interval "b," which equals ejection time (ET), and time interval "d" between the R wave of the ECG and cessation of LV outflow were measured. Thus $MPI = a - b/b$. Isovolumic relaxation time (IRT) was calculated by subtracting time interval "d" from time interval "c," and isovolumic contraction time (ICT) was calculated by subtracting IRT and ET from "a."

Other Doppler and echocardiographic measurements: Peak early (E) and late (A) transmitral filling velocities, E/A

TABLE I Clinical characteristics of cardiac transplant patients

Age (years)	50 ± 9 (21–61)
Sex (male/female No.) (%)	23/1 (96/4)
Cause of transplantation	
Ischemic heart disease (%)	7 (29)
Dilated cardiomyopathy (%)	17 (71)
Number of biopsies/patient	3.5 (1–6)
Biopsy score	
Grade 0	
No. of patients	22
No. of biopsies (%)	60 (61)
Grade IA	
No. of patients	14
No. of biopsies (%)	20 (20)
Grade IB	
No. of patients	14
No. of biopsies (%)	18 (18)
Grade 3A	
No. of patients	1
No. of biopsies (%)	1 (1)
Time from transplantation (months)	1921 (1–81)
Heart rate (beats/min)	89 ± 12 (60–122)
Systolic/ diastolic blood pressure (mmHg)	123 ± 16/ 80 ± 8

FIG. 1 Schema for measurement of myocardial performance index (MPI). The index is defined as the summation of isovolumic contraction time (ICT) plus isovolumic relaxation time (IRT), divided by ejection time (ET) (b). The index is calculated as the ratio of a-b/b. a = time interval between the cessation and onset of mitral inflow, c = time interval between the R wave of the electrocardiogram (ECG) and the onset of the following mitral inflow, d = time interval between the R wave of the ECG and the cessation of left ventricular outflow.

ratio, deceleration time, and the slope of the E wave were measured from the mitral inflow tracings (apical four-chamber view). From the M-mode echocardiogram, the LV posterior wall, septum, and LV dimension at end diastole and end systole were measured. The LV mass was calculated using the Devereux formula,¹⁶ $LV\ mass = 1.04 * [(LVID + PWT + IVST)^3 - (LVID)^3] - 13.6$, where LVID = LV internal dimension in diastole, PWT = posterior wall thickness in diastole, and IVST = interventricular septal thickness in diastole. From the apical four-chamber view, LV ejection fraction (EF) was calculated using a single-plane Simpson's rule algorithm. For analysis of Doppler measurements only, the cycles in which recipient atrial contraction occurred in diastole or early systole were used. Five consecutive beats were measured and averaged for each parameter. All measurements were obtained with the investigator blinded to the result of endomyocardial biopsy.

Endomyocardial biopsy: At least three biopsy specimens of right ventricular endomyocardial tissue were obtained from each patient the same day as the echocardiographic study was performed and graded for rejection according to the International Society for Heart and Lung Transplantation (ISHLT) grading system for acute rejection.^{17, 18} All biopsies were interpreted by one senior cardiac pathologist (EVA) who was blinded to the patient's condition and the results of the echocardiographic study. Only one patient exceeded grade IB throughout the follow-up period.

Reproducibility: Intraobserver variability was assessed in 10 echocardiographic Doppler recordings by repeating the measurements on two occasions 20–30 days apart. To test the interobserver variability, the measurements were performed off line from video recordings by a second observer who was blinded to the results of the first examination.

The ethics committee of our hospital approved the study protocol, and all patients gave informed consent.

Statistical Analysis

Continuous data are expressed as mean value $\pm$ standard deviation (SD). Echocardiographic Doppler indices of cardiac

function were compared with biopsy scores by using one-way analysis of variance (ANOVA) to confirm statistically significant relations between the parameters. The strength of the association between two variables was assessed using Pearson's correlation. The stepwise regression selection technique was used to construct a multivariate model. The receiver operator curve (ROC) was used to determine the relationship between sensitivity and specificity of the test. To analyze the predictive discrimination of the MPI compared with LVEF, the areas under the curve were generated. Statistical (software) Package for Social Sciences for windows (release 10.0) (SPSS, Inc., Chicago, Ill., USA) was used. P values < 0.05 were considered significant.

Results

Patient Characteristics

Of the 24 patients, 23 (94%) were men (mean age 50 ± 9 years, range 21–61 years). Ninety-nine echocardiographic Doppler studies were performed with simultaneous endomyocardial biopsies. The mean time between transplantation and endomyocardial biopsy was 19 months (range 1–81 months), and the mean number of biopsies/patient were 3.5, with a range 1–6. Indications for heart transplantation were ischemic heart disease in 7 patients and dilated cardiomyopathy in 17 patients. The clinical characteristics are summarized in Table I. Sixty endomyocardial biopsies (61%) were considered negative, whereas 20 (20%) showed a biopsy score of IA, 18 (18%) a score of IB, and only 1 (1%) a biopsy score of 3A, which was excluded from statistical analysis. Heart rate was shown not to change significantly with increasing biopsy scores ($p = NS$).

Echocardiographic Doppler Measurements

Left ventricular dimensions and mass did not change significantly (Table II). Ejection fraction is significantly decreased with increasing biopsy score ($48.95 \pm 5.19\%$ in biopsy score

TABLE II Change of echocardiographic indices with increasing biopsy scores in cardiac transplant patients

Biopsy score	0	IA	IB	p < Value
LVID (mm)	48.79 ± 7.23	50.21 ± 5.91	46.87 ± 5.46	NS
LVIS (mm)	28.00 ± 5.83	28.00 ± 4.99	26.69 ± 5.04	NS
IVST (mm)	12.40 ± 2.86	12.43 ± 2.03	13.29 ± 2.06	NS
PWT (mm)	10.31 ± 2.41	11.14 ± 2.38	10.94 ± 1.12	NS
FS (%)	42.71 ± 7.83	44.01 ± 8.56	42.47 ± 10.23	NS
EF (Simpson) (%)	48.95 ± 5.19^a	46.84 ± 4.80	44.47 ± 6.59^a	0.01
LV mass (g)	266.29 ± 99.53	292.32 ± 97.80	267.37 ± 44.44	0.63

Data are mean value $\pm$ standard deviation.

^a Significant difference between biopsy score 0-IB.

Abbreviations: LVID = left ventricular internal dimension in diastole, LVIS = left ventricular internal dimension in systole, IVST = interventricular septal thickness in diastole, PWT = posterior wall thickness in diastole, FS = fraction shortening, EF = ejection fraction, LV = left ventricular.

TABLE III Change of Doppler indices with increasing biopsy scores in cardiac transplant patients

Biopsy score	0	IA	IB	p< Value
ICT (ms)	57.37 ± 18.85 ^b	72.28 ± 17.00 ^b	69.78 ± 23.46	0.005
IRT (ms)	85.86 ± 21.48	85.33 ± 19.80	94.94 ± 28.50	0.304
ICT/ET	0.24 ± 0.09 ^{a, b}	0.31 ± 0.08 ^b	0.31 ± 0.12 ^a	0.002
IRT/ET	0.36 ± 0.10	0.37 ± 0.09	0.43 ± 0.15	0.05
ET (ms)	240.27 ± 25.59	230.10 ± 16.46	225.06 ± 28.31	0.044
MPI	0.60 ± 0.14 ^{a, b}	0.68 ± 0.09 ^b	0.75 ± 0.21 ^a	0.001
E-point velocity (cm/s)	80.77 ± 25.09	82.24 ± 23.90	83.94 ± 26.01	0.92
A-point velocity (cm/s)	36.80 ± 9.88	39.54 ± 8.82	35.25 ± 4.36	0.44
E/A ratio	2.25 ± 0.75	2.12 ± 0.77	2.36 ± 0.76	0.72
Deceleration time (ms)	161.02 ± 31.10 ^a	151.75 ± 25.46	135.45 ± 22.2 ^a	0.028
Deceleration slope (cm/s ²)	531.64 ± 224.02	567.44 ± 216.6	636.82 ± 307.4	0.39
Heart rate (beats/min)	87.16 ± 11.22	89.88 ± 12.77	92.61 ± 12.81	0.22

Data are mean value ± standard deviation.

^a Significant difference between biopsy scores 0–IB.

^b Significant difference between biopsy scores 0–IA.

Abbreviations: ICT = isovolumic contraction time, IRT = isovolumic relaxation time, ET = ejection time, MPI = myocardial performance index.

IA, $46.84 \pm 4.80\%$ in biopsy score IB, $44.47 \pm 6.59\%$ in biopsy score 3A, $p < 0.011$). Analysis of Doppler recordings revealed that ET is also significantly decreased with increasing biopsy score (240.27 ± 25.60 , 230.10 ± 16.46 , and 225.06 ± 28.31 ms, respectively, $p < 0.01$) (Table III). Isovolumic contraction time is significantly prolonged (57.37 ± 18.85 ms in score 0, 72.28 ± 17.00 ms in score IA, and 69.78 ± 23.46 ms in score IB, $p < 0.002$). Isovolumic relaxation time is not significantly altered with increasing biopsy score ($p = \text{NS}$). The ratios of ICT to ET and IRT to ET are significantly increased. Deceleration time is significantly decreased with increasing biopsy scores. The increase of MPI (0.60 ± 0.13 in biopsy score 0, 0.68 ± 0.08 in biopsy score IA, and 0.75 ± 0.20 in biopsy score IB) is highly significant ($p < 0.001$) (Table III). Myocardial performance index is significantly different between biopsy scores 0 and IB (Fig. 2); however, MPI is not different between biopsy scores 0–IA and IA–IB. Multivariate stepwise regression analysis revealed that MPI and deceleration time are the only independent predictors of myocardial biopsy score ($r = 0.48$, $F = 10.53$, $p < 0.0001$). Excluded variables were age, heart rate, E/A ratio, EF, and LV mass.

Myocardial performance index correlates significantly with LV mass ($p < 0.05$) and inversely with E-point velocity, deceleration time ($p < 0.05$), and EF ($p < 0.01$). Multivariate stepwise regression analysis revealed that EF is the only independent predictor of MPI ($r = 0.37$, $F = 9.31$, $p < 0.003$). Excluded

FIG. 2 Change of myocardial performance index ± standard deviation with increasing biopsy score.

variables were age, heart rate, E/A ratio, deceleration time, LV mass, and systolic and diastolic blood pressure.

Table IV summarizes the correlation between variables derived from two-dimensional Doppler analysis with heart rate. Ejection time, IRT, the ICT/ET ratio, and deceleration time were significantly related to heart rate. A significant inverse correlation was observed between LVEF and heart rate. The MPI was independent of heart rate.

TABLE IV Correlation of heart rate with echocardiographic Doppler variables

	EF	DT	E/A	ET	ICT	IRT	MPI
HR	$r = -0.28$ $p = 0.01$	$r = -0.33$ $p = 0.003$	$r = -0.15$ $p = \text{NS}$	$r = -0.62$ $p = 0.0001$	$r = 0.08$ $p = \text{NS}$	$r = -0.25$ $p = 0.02$	$r = 0.15$ $p = \text{NS}$

Abbreviations: HR = heart rate, DT = deceleration time. Other abbreviations as in Tables II and III.

FIG. 3 Receiver operator curve (ROC) analysis of the myocardial performance index (MPI) and ejection fraction (EF) for separation of the presence or absence of mild rejection. The sensitivity and specificity of the MPI are 67 and 67%, respectively. Cut-off point is 0.69. — = Reference line, - - - = MPI, = EF.

Using receiver operating characteristics curve analysis, the MPI yielded an area under the curve of 0.71 ± 0.08 (mean $\pm$ standard error) for separation of patients with or without mild rejection. This was a significantly better predictive discrimination than LVEF (area under the curve 0.33 ± 0.07). The ROC revealed that with a cut-off value 0.69, MPI could predict the biopsy score with 67% sensitivity and 67% specificity (Fig. 3). The intra- and interobserver variability was $< 5\%$.

Discussion

Accurate diagnosis of rejection in cardiac graft transplantation using noninvasive methods still remains a challenge.^{19,20} The development of endomyocardial biopsy has always been considered to be the standard of reference for the diagnosis of rejection by which all other noninvasive methods could be judged. Several attempts to find a Doppler-derived, noninvasive index with high sensitivity and specificity have been made.⁴ Examples include the use of alterations in IRT and pressure half-time with respect to previous baseline examinations. It has been reported that a 15% shortening of IRT or pressure half-time could detect a rejection episode but probably not a mild rejection.²¹ Alterations in peak early (E), late (A) transmitral filling velocities and deceleration time were used as important adjuncts in the echocardiographic follow-up of cardiac transplant patients.¹²

Previous studies reported that during rejection, especially a mild one, systolic function is well preserved.¹³ However, in our study, it was found that while rejection was increasing in severity, EF was reduced and the ET was shortened. This change in systolic indices is not considered clinically important (mean EF $47.58 \pm 5.67\%$). Events in diastole are affected considerably. Isovolumic contraction time is significantly increased with increasing biopsy scores; IRT is not statistically changed. Hauptman *et al.*⁴ and Valantine *et al.*¹² described a significant shortening of the IRT during biopsy-proved rejection. This is probably partly due to the fact that high pressures in the left atrium during rejection tend to open

the mitral valve earlier. In our study, the significant shortening of the ET counterbalances this situation and the overall result is a nonsignificant change of IRT, with increasing rejection. A possible explanation for this change is that, in our study, none of the rejection episodes exceeded mild rejection.²² During isovolumic time intervals, two energy-consuming processes are taking place:²³ the release of ionic Ca^{++} from the cardiac sarcolemma and the formation of actin-myosin bridges during ICT, and the reuptake of ionized Ca^{++} in the cardiac sarcolemma during IRT. Early myocardial dysfunction affects these phenomena, thus resulting in ICT and IRT alterations. All these alterations combined are reflected in MPI (or Tei-index).^{24,25}

Myocardial Performance Index

In our study, this index could discriminate between no rejection and mild rejection with 67% sensitivity and 67% specificity (cut-off value of MPI = 0.69). This should be taken into consideration since the majority of mild rejection episodes is asymptomatic, usually undiagnosed with the current noninvasive methods, and can evolve into serious rejection.²² Moreover, the index may be of particular importance when considering concomitant infection, particularly when endomyocardial biopsy is not readily available. This borderline specificity may be due to several factors, such as factors related to biopsy sampling error with failure to detect more advanced rejection in some cases or the possibility that humoral rejection had occurred during several episodes of allograft rejection.⁴ Long-standing cardiac dysfunction, mainly due to coronary atherosclerosis and its complications,²⁶ was excluded by routinely performing coronary angiograms every year and evaluating echocardiographic parameters such as EF and myocardial motility. Immunosuppressive treatment does not seem to affect the results since all patients were on the same regimen. Because most clinical and noninvasive laboratory parameters of cardiovascular decompensation have low specificity, a combination of two or more abnormal findings was required before clinically significant allograft dysfunction was considered present.

The aim of the current study was to focus on the evaluation of MPI with respect to rejection severity. Multivariate regression analysis revealed that MPI was the strongest independent correlate of endomyocardial biopsy score, with deceleration time in the second position. In our study population, conventional parameters of diastolic function (the early-to-late peak velocities ratio, IRT) did not change significantly with rejection severity score. These findings may be mainly attributed to "pseudonormalization" of the mitral inflow. Other parameters, which changed significantly with increasing biopsy scores such as the ICT/ET ratio, deceleration time and EF were significantly related to heart rate, and this limits the daily clinical use.

Myocardial performance index shows no correlation with heart rate²⁷ and was independent of systolic and diastolic blood pressure in our study. Furthermore, MPI is not affected by ventricular geometry.²⁸ The index seems to be relatively in-

dependent of alterations in preload²⁹ and afterload³⁰ and the degree of mitral regurgitation,⁷ which was only mild in the study patients. Myocardial performance index has already been studied in a variety of diseases, such as dilated cardiomyopathy,^{7,8} amyloidosis,⁶ and pulmonary hypertension,⁹ where MPI correlates with the severity of the disease and has predictive value for the outcome. It seems also useful in the diagnosis and follow-up of congenital heart diseases, the acute phase of myocardial infarction,³¹ congestive heart failure,³² and pediatric cardiac transplant patients.³³ In this last study, despite the limited number of patients studied, the authors conclude that Tei-index, when applied to the left ventricle, may serve as a predictor of moderate rejection in pediatric transplant patients. Recently, investigators applied MPI to adult cardiac transplant patients. They indicated a statistically significant change of MPI between nonrejection and moderate rejection and they recommend the use of a 20% change of MPI to detect moderate cardiac allograft rejection.³⁴ It seems that MPI can allow for an even earlier diagnosis of myocardial rejection, when it is still only mild and the patients may present with subtle and ambiguous symptoms.

Though MPI may not yet replace endomyocardial biopsy for the detection of mild rejection, in the event of an unexpected finding during a routine study, early biopsy can be recommended. A higher MPI in the setting of a normal biopsy could suggest a sampling error, partially treated rejection, or incipient rejection, and an urgent biopsy would be warranted. Discrepancies between biopsy results and MPI findings warrant close clinical follow-up and repeat evaluations. In our clinical practice, if there is clinical suspicion of rejection at any time, an echocardiographic Doppler study can be performed, and if MPI and other echocardiographic parameters, such as IRT and pressure half time, indicate rejection, a biopsy is recommended and performed promptly without waiting for the routinely scheduled biopsy.

Limitations

In the current study, the MPI was calculated only in patients referred for endomyocardial biopsy. Patients with atrial fibrillation, pacemakers, bundle-branch block, or high-grade atrioventricular block were excluded from the study. Specifically, with regard to rejection in the transplant patient, the use of MPI is limited by variability in contribution to transmitral flow by the function and size of the recipient atrium, timing of the study (especially in the early post-transplant period), and interpretation in the setting of discordance with biopsy results. In our study, there was only one case with biopsy score > 0 during the early post-transplantation period. This limited number does not allow for reliable statistical analysis of the results to compare "early" versus "late" post-transplantation period.

Conclusion

Myocardial performance index seems to be a promising method for use in the follow-up of cardiac transplant patients.

The present data suggest that a further study is needed to clarify the utility of the myocardial performance index in predicting rejection in cardiac transplant patients.

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Images in Cardiology: Isolated Pulmonary Arterial Pulsus Alternans Secondary to Pulmonary Hypertension

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FIG. 1 Transthoracic echocardiogram demonstrating marked enlargement of the right ventricular (RV) cavity, ventricular septum (VS) flattening, and a "D"-shaped left ventricle (LV).

A 32-year-old female with an undifferentiated connective tissue disease and progressive dyspnea underwent echocardiography (Fig. 1), followed by right heart catheterization (Fig. 2).

FIG. 2 Pulmonary arterial (PA) pressure tracing demonstrating pulmonary hypertension with pulmonary artery pulsus alternans.

Pulsus alternans, described by Traube in 1872, is a regular alternation in pulse pressure amplitude. This pattern may occur independently or simultaneously in the systemic and pulmonary circulations. Although seldom described, pulmonary artery pulsus alternans is not uncommon. Clinical significance, apart from the degree of right heart failure, is uncertain.