The prognostic value of tricuspid valve annular motion in large malignant pericardial effusions.

Antonis Samaras¹, Eftychios Siniorakis¹, Antonis Ziakas,
Stavros Gavriilidis², Konstantinos Gemitzis²

¹Department of Cardiology, Sotiria Chest Diseases Hospital, Athens
²1st Cardiology Department, AHEPA University Hospital, Aristotle University of Thessaloniki, Greece

ABSTRACT: Background and objectives: Although collapsing of the right atrium (RA) and/or right ventricle (RV), as far as flow velocity paradox through the tricuspid valve (TV), are common findings in the echocardiogram (ECHO) of threatened tamponade, their prognostic value remains controversial. We investigated whether an interrogation of the TV annular motion offers any additional prognosticators in cases of large malignant pericardial effusions (PE).

Subjects and methods: 96 patients with newly diagnosed lung cancer and neoplastic PE, not in clinical tamponade, underwent a respirophasic conventional and tissue Doppler imaging (TDI) of the TV annulus. Ra and RV collapsing, TV annular plane systolic excursion (TAPSE), and TV annular velocities Sa, Ea, Aa were assessed. In a period of one month, 37 patients (group A) developed clinical tamponade, versus 59 patients (group B) who did not. The independent value of each ECHO parameter in predicting tamponade was estimated by univariate and multivariate analysis.

Results: Collapsing of Ra and RV were more frequent in group A (84% vs 69% and 41% vs 20% respectively), whereas the trans-tricuspid flow velocity paradox was similar in both groups. TAPSE and Sa were higher in group A (p < 0.001). The velocities Ea and Aa demonstrated an excessive respirophasic fluctuation (ΔEa and ΔAa), with inspiratory increase and expiratory decrease. ΔEa and ΔAa were higher in group A (p < 0.001). In multivariate analysis, TAPSE, expiratory Ea and Aa, as well as ΔAa, were independent predictors of tamponade.

Conclusion: Large neoplastic PE manifest an enhanced longitudinal motility of TV annulus. Early progression to tamponade is likely, and parameters deriving from the TDI of the RV free wall present considerable predictive value.

Key Words: Malignant pericarditis, Cardiac tamponade, Tricuspid annulus, Tissue Doppler imaging, Prognosis.

INTRODUCTION

When a large pericardial effusion (PE) exerts constriction against the myocardium, an abnormal transvalvular respiratory fluctuation of the flow velocities may appear. This phenomenon, known as flow velocity paradox, is easily interrogated by the echocardiogram (ECHO), mainly in the transmitral and transtricuspid pulse Doppler diastolic signal¹². In this instance, velocity through the tricuspid valve (TV) increases during inspiration and decreases in expiration, displaying a respiratory fluctuation of more than 40%. A reciprocal respirophasic event takes place in the transmitral velocities³.

Right cardiac chambers, because of their subtle muscular wall and low intracavitary pressure, are the first to suffer constraint phenomena by PE, expressed as diastolic invaginations or collapsing⁴. These ECHO features, although alarming, are not synonymous of tamponade, which remains a pure clinical event⁵⁶. However, the prognostic value of right atrium (RA) or right ventricle (RV) invaginations and TV flow velocity paradox, in predicting tamponade is uncertain⁷⁸.

It has been observed recently that when the lateral expansion of the heart is obstructed, due to pericardial diseases, longitudinal hypermotility appears in order to facilitate the diastolic filling of the heart. This
compensatory mechanism is detected by tissue Doppler imaging (TDI) of the cardiac base, which demonstrates unexpectedly high dynamics during diastole (annular paradox). The prototype of this scenario has been encountered in constrictive pericarditis. In this setting, the mitral annulus TDI displays high protodiastolic velocities Ea, which recently were found to represent respirophasic fluctuations analogous to that of the transmitral early diastolic velocity E1. If tamponade, which shares many common ECHO characteristics with constrictive pericarditis, presents TDI features similar to the above described, remains uncertain. Especially when referring to right ventricular longitudinal motion during tamponade, data is extremely scarce, although right cardiac chambers are the first victims of pericardial constraint phenomena.

In this prospective study we sought to interrogate the tricuspid annular features in patients with large malignant PE, in parallel with other classic ECHO signs of right heart compromise. Furthermore, we checked the prognostic value of each right heart related ECHO parameter in predicting tamponade.

PATIENTS AND METHODS

Ninety six consecutive patients (male 61, female 35, aged 67 ± 13 years) with newly diagnosed lung cancer, accompanied by large PE (> 2 cm) in their computerized chest tomograms, and referred for an ECHO-based haemodynamic assessment, were included. Dyspnoea, cough and chest pain were the principal symptoms upon admission. No patient was in clinical tamponade. A comprehensive ECHO comprising M-mode, 2D, pulsed wave Doppler and TDI was performed, using a GE Vivid Vingmed 7 machine (Horton, Norway) and a 1.5-4 MHz transducer. The following conventional parameters were calculated under respirophasic synchronization: left ventricular (LV) ejection fraction (EF) by Simpson’s rule, RV systolic pressure whenever TV regurgitation was detected (this was possible in 87 patients), early and late trans-tricuspid diastolic velocities E and A, their respirophasic fluctuations ΔE and ΔA, and finally TV annular plane systolic excursion (TAPSE). ΔE and ΔA were calculated subtracting the lowest velocity value from the highest and dividing by the lowest1,12. TAPSE was measured by M-mode recordings from the apical four chamber view, placing the cursor at the free lateral corner of the TV annulus. RA and RV collapse, when they were encountered, were synchronized with the electrocardiogram, as was the case with the maximal PE diameter, which was measured in diastole. For the TDI of RV, a 4- to 6-mm sampling gate was placed at the lateral margin of the TV annulus, and the peak systolic velocity (Sa) as well as the early and late diastolic velocities Ea and Aa respectively were measured, paying attention to their respirophasic behavior. The exclusion criteria were as follows: chronic obstructive pneumonopathies, atrial fibrillation, known heart diseases and/or use of cardiovascular medication, TV regurgitation more than mild, swinging heart, localized PE, circumferential PE with diameter < 2 cm, and finally thick pericardial layers detected in the chest computerized tomography or the ECHO. The study was approved by the institution’s research ethical committee and all patients gave written informed consent.

After the baseline ECHO was completed, given that no patient was in tamponade, the decision for pericardial drainage was taken by the oncologists and thoracic surgeons who managed the underlying disease of lung cancer. Meanwhile, patients were under strict surveillance and an ECHO was repeated every 5 days, until a programmed or urgent drainage of PE had to take place. Patients with acute clinical deterioration underwent emergency ECHO and ECHO-guided pericardiocentesis. The follow-up lasted one month, and as end point was considered the appearance of clinically overt tamponade. At the end of the follow-up 37 patients (men: 20, women: 17) had developed tamponade and constituted group A. The tamponade was manifested by worsening dyspnoea, and a drop of arterial blood pressure with pulsus paradoxus, and took place 16 ± 8 days after our initial contact with the patient. All patients in group A had pericardiocentesis with a yield of 750 ± 120 ml of bloody fluid. Cytologic examination of the fluid confirmed the neoplastic nature of the PE. No patient died of tamponade or pericardiocentesis. The remaining 59 patients (men: 30, women: 29) had no tamponade until the end of the follow-up period, and constituted group B. Their PE were drained at a later stage, during programmed lung surgery.

For the statistical analysis, continuous variables were expressed as mean ± SD. Differences between
the groups were assessed by the unpaired t-test for continuous variables and the chi-square test for categorical variables. Parameters were considered for univariate statistical significance, using the Cox proportional hazard model. Variables with \( p < 0.1 \) were then included in the multivariate Cox model to determine which of them were independently related to the prognosis of tamponade. In the final regression model, variable at \( p < 0.05 \) level of significance were retained (Wald test). P values were calculated by the log-rank test. All the analyses were performed using a commercially available statistical programme (SPSS 15.1).

**RESULTS**

Individual characteristics and ECHO findings of the whole cohort of 96 patients appear in Table 1 (first column). LV was of normal function and no signs of pulmonary hypertension were detected. RA end-diastolic and end-systolic collapse were observed in 75% of all cases, while diastolic RV collapse was noticed in 28% of them. The TV flow velocity paradox was 26% for the velocity E, and 11% for the velocity A. Regarding the TDI of the TV annulus, the early diastolic velocity Ea showed a respirophasic fluctuation of 38% and the late diastolic velocity Aa a fluctuation of 41%.

| Table 1. Baseline characteristics of the patients as a whole and when divided in groups. |
|--------------------------------|----------------------------|----------------|----------------|--------|
| Characteristic               | Whole cohort               | Group A        | Group B        | p      |
| Age (Years)                  | 65.0 ± 11.9                | 64.4 ± 11.1    | 66.5 ± 12.5    | 0.434  |
| PE diam (cm)                 | 2.3 ± 0.4                  | 2.5 ± 0.3      | 2.4 ± 0.4      | 0.414  |
| LVEF (%)                     | 63.8 ± 6.3                 | 65.1 ± 6.4     | 63.0 ± 6.1     | 0.140  |
| Einsp (cm/s)                 | 67.6 ± 10.4                | 63.3 ± 10.3    | 70.2 ± 9.6     | 0.001  |
| Eexp (cm/s)                  | 54.5 ± 10.9                | 50.0 ± 10.4    | 57.7 ± 10.3    | 0.001  |
| ΔE (%)                       | 26.0 ± 18.1                | 28.9 ± 19.1    | 24.1 ± 17.3    | 0.209  |
| Ainsp (cm/s)                 | 62.9 ± 11.4                | 61.6 ± 11.3    | 63.8 ± 11.3    | 0.363  |
| Aexp (cm/s)                  | 57.1 ± 10.6                | 54.6 ± 9.7     | 58.5 ± 10.9    | 0.080  |
| ΔA (%)                       | 11.0 ± 12.7                | 13.9 ± 19.6    | 9.2 ± 4.1      | 0.081  |
| TAPSE (cm)                   | 2.5 ± 0.8                  | 3.3 ± 0.6      | 2.1 ± 0.3      | < 0.001|
| RVSP (mmHg)                  | 35.4 ± 6.4                 | 34.2 ± 6.7     | 36.3 ± 6.1     | 0.144  |
| Sa (cm/s)                    | 14.7 ± 4.2                 | 18.7 ± 3.1     | 12.2 ± 2.6     | < 0.001|
| Ea insp (cm/s)               | 11.9 ± 4.9                 | 17.8 ± 3.6     | 8.7 ± 2.1      | < 0.001|
| Ea exp (cm/s)                | 8.5 ± 2.9                  | 11.0 ± 2.4     | 6.9 ± 1.8      | < 0.001|
| ΔEa (%)                      | 37.7 ± 18.6                | 56.1 ± 13.6    | 26.1 ± 9.8     | < 0.001|
| Aa insp (cm/s)               | 17.0 ± 7.6                 | 25.2 ± 5.4     | 11.8 ± 2.6     | < 0.001|
| Aa exp (cm/s)                | 11.9 ± 4.8                 | 16.2 ± 4.6     | 9.1 ± 2.2      | < 0.001|
| ΔAa (%)                      | 41.1 ± 20.4                | 57.9 ± 19.1    | 30.5 ± 12.6    | < 0.001|

Data are expressed as mean values ± standard deviation. PE diam: pericardial effusion diameter, LVEF: left ventricular ejection fraction, Einsp and Eexp: transtricuspid E velocity in inspiration and expiration, ΔE: respirophasic fluctuation of E, Ainsp and Aexp: transtricuspid A velocity in inspiration and expiration, ΔA: respirophasic fluctuation of A, TAPSE: tricuspid annular plane systolic excursion, RVSP: right ventricular systolic pressure, Sa: peak systolic tricuspid annular velocity; Ea insp and Ea exp: early diastolic tricuspid annular velocity in inspiration and expiration, ΔEa: respirophasic fluctuation of the Ea, Aa insp and Aa exp: late diastolic tricuspid annular velocity in inspiration and expiration, ΔAa: respirophasic fluctuation of the Aa.
The increase in velocities was noted exclusively in inspiration i.e. in phase with the transtricuspid flow velocities.

Comparison between groups A and B, are shown in the last two columns of Table 1. These two groups were similar regarding the age of patients, PE diameter and LVEF. RA collapse was encountered in 84% of group A patients compared to 69% of group B. RV diastolic collapse was found in 41% vs 20% in groups A and B respectively. Compared to group B, patients in group A had lower values of transtricuspid velocity E, in both phases of respiration (Einsp = 63.3 ± 10.3 cm/s vs 70.2 ± 9.6 cm/s, and Eexp = 50.0 ± 10.4 cm/s vs 57.7 ± 10.3 cm/s, p < 0.001), whereas late diastolic velocities A did not differ. The respirophasic fluctuations of both E and A velocities, were similar in both groups.

RV free wall behavior along the longitudinal axis, was more intense in group A. Thus, group A had higher TAPSE values (3.3 ± 0.6 cm vs 2.1 ± 0.3 cm, p < 0.001). The enhanced longitudinal motion of group A, was evident in the higher values of Sa (18.7 ± 3.1 cm/s vs 12.2 ± 2.6 cm/s, p < 0.001) as well as the higher velocities Ea (Ea insp = 17.8 ± 3.6 cm/s vs 8.7 ± 2.1 cm/s, p < 0.001, and Ea exp = 11.0 ± 2.4 cm/s vs 6.9 ± 1.8 cm/s, p < 0.001), and Aa (Aa insp = 25.2 ± 5.4 cm/s vs 11.8 ± 2.6 cm/s, p < 0.001 and Aa exp = 16.2 ± 4.6 cm/s vs 9.1 ± 2.2 cm/s, p < 0.001). The respiratory fluctuations of the diastolic annular velocities were also higher in group A (ΔEa = 56.1 ± 13.6% vs 26.1 ± 9.8%, p < 0.001 and ΔAa = 57.9 ± 19.1% vs 30.5 ± 12.6%, p < 0.001).

Independent predictors of tamponade appear in Table 2. When assessed by univariate analysis, the fol-
lowing classic ECHO factors were found to independently predict tamponade: RV collapse (HR = 2.02%, 95% CI = 1.05-3.90), Einsp (HR = 0.95, 95% CI = 0.91-0.98), Eexp (HR = 0.95, 95% CI = 0.93-0.98), ΔA (HR = 1.02, 95% CI = 1.01-1.04) and TAPSE (HR = 4.49, 95% CI = 3.08-6.54). However, when multivariate analysis was performed for the classic ECHO parameters, only TAPSE maintained a significant prognostic value (HR = 2.94, 95% CI = 1.74-4.98).

From the RV TDI, in the univariate analysis, independent predictors for a forthcoming tamponade were the following parameters: Sa (HR = 1.22, 95% CI = 1.16-1.29), Ea insp (HR = 1.40, 95% CI = 1.29-1.52), Ea exp (HR = 1.69, 95% CI = 1.47-1.94), ΔEa (HR = 1.06, 95% CI = 1.05-1.08), Aa insp (HR = 1.13, 95% CI = 1.09-1.16), Aa exp (HR = 1.13, 95% CI = 1.09-1.17) and ΔAa (HR = 1.04, 95% CI = 1.03-1.06). In the multivariate analysis, only the expiratory values of Ea (HR = 1.49, 95% CI = 1.29-1.78) and Aa (HR = 1.12, 95% CI = 1.04-1.21) as far as Δa (HR = 1.03, 95% CI = 1.02-1.05) maintained their independent prognostic value.

Figures 1 and 2 show an example of standard and TDI ECHO findings in a patient of group A, who developed tamponade 8 days later. TAPSE and excessive respiraphasic fluctuations in transtricuspid and Ea velocities are shown.

**DISCUSSION**

**Annular paradox extended to tricuspid annulus**

Every time myocardial damage occurs, TDI of free ventricular walls displays diminished values of systolic as well as diastolic annular velocities. Contrarily, in some pericardial diseases, mainly in constrictive pericarditis, where participation of the myocardium is negligible or non-existent, increased values of Ea have been observed, although this phenomenon known as annular paradox was almost exclusively studied in mitral annulus. Whether a similar event occurs or the RV annulus is implicated, in threatened or established tamponade, it is far less known. In this study, we found high Ea and TAPSE values in the group that developed tamponade. The likely explanation for this phenomenon is that as the lateral dilatation of the RV is reduced, because of constraint phenomena exerted by large PE, the longitudinal motion is increased. This hypermotility was reflected in this study, into unexpectedly high values of RV diastolic annular velocities.

![Figure 1. Tricuspid annular plane systolic excursion (TAPSE) in a patient of group A, given by the distance between the two dotted horizontal lines, measuring 3.1cm.](image1.png)

![Figure 2. Same patient as Figure 1. Top: Respiratory transtricuspid flow velocity paradox. The diastolic velocities E and A increase excessively in inspiration and decrease in expiration (fluctuation corresponding to 48% of the expiratory value). Bottom: In-phase respiraphasic variation of the tricuspid annular tissue Doppler velocities. The early diastolic Ea velocity increases in inspiration and decreases in expiration (fluctuation corresponding to 85% of the expiratory value). The late diastolic velocity Aa remains rather unaltered in this example.](image2.png)
Respirophasic fluctuations of RV diastolic annular velocities

Although respirophasic fluctuations of transtricuspid diastolic velocities are common in threatened tamponade, such a phenomenon in RV diastolic annular velocities has not been observed, with the exception of some rare case reports\(^1\). Annular velocities are considered load-independent\(^2\). Thus, a raising of RV Ea and/or Aa during inspiration, when venous return corresponding to RV preload increases, constitutes another paradox. Sohn DW and coauthors had first observed an analogous phenomenon in mitral annular velocities, in cases of constrictive pericarditis\(^1\). In the very few cases of tamponade, reported by the same authors, this was not observed, and the possibility of respirophasic behavior of RV lateral annular wall was not tested.

It is not easy to assign a credible explanation to a respirophasic annular pattern. However, the appearance of such a phenomenon in our study was an ominous predictor of imminent tamponade. In other words, when preload starts influencing the RV annular diastolic motion, giving a priority to the inspiratory filling, the exhaustion of the longitudinal compensatory mechanisms has already started.

The questionable prognostic value of classic ECHO parameters

Although RA and RV invaginations and transtricuspid flow velocity paradox are the ECHO phenomena which attract most attention in cases of threatened tamponade, their prognostic value remains uncertain.\(^7\)\(^8\)\)

In this study, the above mentioned ECHO parameters showed a considerable predictive value in univariate analysis. However, when a multivariate analysis was used, only factors related to the RV longitudinal motion were found to be authentic prognosticators.

Nature of the PE and speed of tamponade development

Little is known about the speed of tamponade development. It seems that nearly one third of patients with large idiopathic PE develop cardiac tamponade unexpectedly, and some experts recommend that asymptomatic PE > 20mm should be drained, if persisting for more than a month\(^1\).\(^2\). Concerning malignant PEs, especially when they are large, it is considered that they carry a high probability of deterioration into tamponade\(^2\).\(^2\). When the diameter of a malignant PE is 1.0-2.0 mm, under conservative treatment, then the probability of tamponade development is 20% over a 2 month period\(^3\).

study limitations

Only malignant PE secondary to lung neoplastic diseases were recruited to this study. Therefore it is not certain if the findings are applicable to PEs of other causes. ECHO phenomena potentially related to constraining of the left cardiac chambers, were not studied, and our interest was focused on right heart chambers. This detracted from the appreciation of the heart function as a whole organ. There was no ECHO follow up, after PE drainage, so there is no data concerning the recurrence of PE and associated ECHO parameters. Moreover, some of these findings are similar to those observed in cases of constrictive pericarditis. The exclusion of pericardial constriction, apart from the PE, was based on the absence of thick pericardial layers on ECHO and computerized chest tomography. Even so, the possibility of effusive-constrictive pericarditis, causing constriction characteristics on ECHO, cannot be ruled out categorically. Invasive haemodynamic assessment would have given, perhaps, an answer.

Conclusion

A high percentage of patients with lung cancer and large malignant PE proceed to tamponade in a rather short period of time. RV annular motion is enhanced in this cohort, with diastolic velocities presenting respirophasic fluctuations in-phase with the transtricuspid ones. Simple ECHO indices, related to tricuspid systolic excursion, and TDI indices from the RV free lateral wall, are of significant prognostic value in predicting tamponade, and merit further investigation.
ΠΕΡΙΛΗΨΗ
Σκοπός: Η παράδοξη αναπνευστική διακύμανση ταχυτήτων δια της τριγλώχινος βαλβίδος (TB) είναι μεν συχνή στο ηχωκαρδιογράφημα (ΗΧΩ) ασθενών με επαπειλούμενο επιπωματισμό, αλλά με ασαφή προγνωστική αξία. Υποθέσαμε ότι η επιμήκης κινητικότητα της TB θα προσέφερε περαιτέρω προγνωστικούς δείκτες σε περιπτώσεις σοβαρών κακοήθων περικαρδιακών συλλογών (ΠΣ).

Μέθοδοι: Ενενήντα έξι ασθενείς με νεοπλασίες πνευμόνων και σοβαρές ΠΣ, χωρίς επιπωματισμό, εκτιμήθηκαν με κλασσικό ΗΧΩ και παλμικό ιστικό Doppler (TDI) του τριγλωχινικού δακτυλίου. Μελετήθηκε η αναπνευστική διακύμανση ταχυτήτων διά της TB, η συστολική μετατόπιση (TAPSE) και οι ταχύτητες Sa, Ea και Aa του δακτυλίου της TB. Εντός μηνός, 37 ασθενείς (ομάδα Α) εξεδήλωσαν επιπωματισμό, έναντι 59 ανεπίπλεκτων ασθενών (ομάδα Β). Με πολυπαραγοντική ανάλυση εκτιμήθηκε η ανεξάρτητη προγνωστική αξία εκάστου ΗΧΩ ευρήματος ως προς την επέλευση του επιπωματισμού. Υπολογίσθηκαν η αναλογία κινδύνου (hazard ratio, HR) και τα διαστήματα εμπιστοσύνης (confidence intervals, CI).

Αποτελέσματα: Η αναπνευστική διακύμανση ταχυτήτων ήταν παρόμοια στις δύο ομάδες. Η TAPSE ήταν υψηλότερη στην ομάδα Α (3.3 ± 0.6 cm έναντι 2.1 ± 0.3 cm, p < 0.001) καθώς και η Sa (18.7 ± 3.1 cm/s έναντι 12.2 ± 2.6 cm/s, p < 0.001). Οι ταχύτητες Ea και Aa εμφανίζαν παθολογικές αναπνευστικές διακυμάνσεις (ΔΕa και ΔΑa αντίστοιχα), αυξανόμενες κατά την εισπνοή και μειούμενες κατά την εκπνοή. Η ΔΕa ήταν υψηλότερη στην ομάδα Α (56.1 ± 13.6% έναντι 26.1 ± 9.8%, p < 0.001) καθώς και η ΔΑa (57.9 ± 19.1% έναντι 30.5 ± 12.6%, p < 0.001). TAPSE (HR = 2.94, 95% CI = 1.74 - 4.98) και ΔAa (HR = 1.03, 95% CI = 1.02 - 1.05) αναδείχθηκαν ανεξάρτητοι προγνωστικοί παράγοντες επιπωματισμού.

Συμπέρασμα: Ο δακτύλιος της TB εμφανίζει αυξημένη κινητικότητα σε ασθενείς με μεγάλες κακοήθεις ΠΣ ενώ το TDI του παρέχει αξιόλογους προγνωστικούς δείκτες σε προς την επέλευση του επιπωματισμού. Λέξεις Κλειδιά: Κακοήθης περικαρδίτις, Καρδιακός επιπωματισμός, Τριγλωχινικός δακτύλιος, Παλμικό Ιστικό Doppler, Πρόγνωση.

REFERENCES

9. Ha JW, Oh JK, Ling LH, Nishimura RA, Seward JB,


