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Anthracycline-Induced Cardiotoxicity: Cardiac Monitoring by Continuous Wave-Doppler Ultrasound Cardiac Output Monitoring and Correlation to Echocardiography

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Keywords
Cardiotoxicity · Anthracyclines · CW-Doppler · USCOM · Ultrasound · NT-pro-BNP · hs-Troponin T

Summary
Background: Anthracyclines are agents with a well-known cardiotoxicity. The study sought to evaluate the hemodynamic response to an anthracycline using real-time continuous-wave (CW)-Doppler ultrasound cardiac output monitoring (USCOM) and echocardiography in combination with serum biomarkers. **Methods:** 50 patients (26 male, 24 female, median age 59 years) suffering from various types of cancer received an anthracycline-based regimen. Patients' responses were measured at different time points (T0 prior to infusion, T1 6 h post infusion, T2 after 1 day, T3 after 7 days, and T4 after 3 months) with CW-Doppler ultrasound (T0–T4) and echocardiography (T1, T4) for hemodynamic parameters such as stroke volume (SV; SV_{USCOM} ml) and ejection fraction (EF; $EF_{echocardiography}$%) and with NT-pro-BNP and hs-Troponin T (T0–T4). **Results:** During the 3-month observation period, the relative decrease in the EF determined by echocardiography was –2.1% (ΔT0–T4, T0 71 ± 7.8%, T4 69.5 ± 7%, p = 0.04), whereas the decrease in SV observed using CW-Doppler was –6.5% (ΔT0–T4, T0 54 ± 19.2 ml, T4 50.5 ± 20.6 ml, p = 0.14). The kinetics for serum biomarkers were inversely correlated. **Conclusions:** Combining real-time CW-Doppler USCOM and serum biomarkers is feasible for monitoring the immediate and chronic hemodynamic changes during an anthracycline-based regimen; the results obtained were comparable to those from echocardiography.

* Sandra Geiger and Sophia Horster contributed equally to this work.

Schlüsselwörter
Kardiotoxizität · Anthrazykline · CW-Doppler · USCOM · Ultraschall · NT-pro-BNP · hs-Troponin T

Zusammenfassung
Hintergrund: Anthrazykline sind Substanzen mit einer bekanntermaßen hohen Kardiotoxizität. Diese Studie hatte zum Ziel, die hämodynamischen Veränderungen unter einem Anthrazyklin mittels Continuous-Wave (CW)-Doppler-Ultraschall-Herzauswurf-Monitoring (USCOM) und Echocardiographie sowie mit Serumbiomarkern vergleichend zu untersuchen. **Methoden:** 50 Patienten (26 Männer, 24 Frauen, medianes Alter 59 Jahre) mit verschiedenen Krebserkrankungen erhielten eine Anthrazyklin-basierte Therapie. An verschiedenen Untersuchungszeitpunkten (T0 vor Infusion, T1 6 h nach Infusion, T2 nach 1 Tag, T3 nach 7 Tagen, und T4 nach 3 Monaten) wurden mittels CW-Doppler Ultraschall (T0–T4) und Echokardiographie (T1, T4) hämodynamische Parameter wie Schlagvolumen (SV_{USCOM} ml) und Ejektionsfraktion ($EF_{Echokardiographie}$%) sowie Kinetiken von NT-pro-BNP und hs-Troponin T erfasst (T0–T4). **Ergebnisse:** Während der 3-monatigen Beobachtungszeit betrug der relative Abfall der EF in der Echokardiographie –2,1% (ΔT0–T4, T0 71 ± 7,8%, T4 69,5 ± 7%, p = 0,04) wohingegen das mit USCOM bestimmte SV CW-Doppler um –6,5% fiel (ΔT0–T4, T0 54 ± 19,2 ml, T4 50,5 ± 20,6 ml, p = 0,14). Eine inverse Korrelation wurde bei der Kinetik der Biomarker beobachtet. **Schlussfolgerung:** Mit dem CW-Doppler-basierten USCOM-Verfahren sowie mit Biomarkern lassen sich die akuten und chronischen Veränderungen der Hämodynamik unter einer Anthrazyklin-haltigen Therapie erfassen. Die Ergebnisse sind vergleichbar mit denen der Echokardiographie.

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Introduction

Cytostatic antibiotics of the anthracycline class are chemotherapeutics that are notorious for causing cardiac side effects [1]. Since these novel cancer therapies have improved the long-term survival of patients with malignancies, the importance of their adverse early- and particularly late-onset cardiovascular effects is increasing.

Cardiac events may include symptomatic or asymptomatic blood pressure changes, thrombosis, electrocardiographic changes, arrhythmias, myo-pericarditis, myocardial infarction, cardiomyopathy, cardiac failure (especially left ventricular failure) and congestive heart failure [2]. These may occur within days or weeks after treatment, or sometimes within months or years after termination of chemotherapy. Cardiac damage caused by anthracyclines cannot be attributed to their anti-cancer mechanisms. As the heart is a post-mitotic organ, the only mechanism of adaptation and/or repair is hypertrophy of the remaining myocardium [3, 4].

The intention of routine cardiac monitoring during a potentially cardiotoxic chemotherapy regimen is the early detection of restricted cardiac function and, as a consequence, a dose reduction or termination of cardiotoxic treatments. The most specific method for diagnosing myocardial changes during treatment with anthracyclines is endomyocardial biopsy [3, 5, 6]. However, there are non-invasive methods of cardiac monitoring that are more established in clinical routine, such as radionuclide ventriculography and echocardiography. The latter is recommended by the ACC (American College of Cardiology), the AHA (American Heart Association) and the ASE (American Society of Echocardiography) for cardiac monitoring of patients receiving anthracyclines [7, 8].

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are important serological parameters for diagnosis, prognosis and response to treatment in patients with acute or chronic heart failure [9–14]. ANP and BNP are cleaved from the C-terminal end of their pro-hormones pro-BNP/pro-ANP and are released into the circulation together with the corresponding N-terminal fragment (N-terminal pro-BNP/NT-pro-BNP, N-terminal pro-ANP/NT-pro-ANP). In heart failure, ANP and BNP release is correlated to the ventricular filling pressure. The plasma concentrations increase during clinical symptomatic or asymptomatic systolic or diastolic dysfunction [16].

Cardiac troponins are proteins with 3 subunits: troponin T (cTnT), troponin I (cTnI) and troponin C. Cardinale et al. showed that, during treatment with chemotherapy, elevated levels of troponin are associated with a decrease of left ventricular (LV) ejection fraction (EF). In contrast, patients with no elevation of troponin levels during chemotherapy may show a transient reduction of LVEF, which returns to baseline during the long-term follow-up [17–20]. cTnI is a specific and sensitive marker for myocardial damage and can be suggestive for the extent of left ventricular dysfunction in an early stage of therapy [21, 22].

Ultrasound cardiac output monitoring (USCOM; USCOM Pty Ltd, Sydney, Australia) is a non-invasive hemodynamic monitoring system based on continuous-wave (CW) Doppler principle with a transportable touch-screen monitor and 2.2-MHz ultrasound probe. Knobloch and co-workers have shown that combining real-time CW-Doppler ultrasound and serum biomarkers is a feasible method for monitoring the hemodynamic changes to cardiotoxic agents like the anthracyclines or trastuzumab [23, 24].

The aim of our pilot study was to evaluate the hemodynamic response to the anthracyclines with real-time CW-Doppler USCOM and echocardiography in combination with serum biomarker kinetics over a period of 3 months.

Patients and Methods

Patients

Fifty patients from the Ludwig-Maximilians University hospital, Munich, Germany were enrolled prospectively into this pilot study. The study protocol was approved by the institutional ethics committee. Informed consent was given by the patient prior to study entry. Data were evaluated descriptively.

Patients receiving a first-line anthracycline (and/or mitoxantrone) -based regimen for hematological malignancies or a solid tumor were eligible. Patients were required to have a Karnofsky Performance Status (KPS) of ≥70% and to be between 18 and 65 years old. Patients who had a positive history of coronary heart disease with cardiac dysfunction (> NYHA I), or an impaired LVEF were not eligible; cardiac EF by echocardiography had to be normal (EF 50%) prior to study entry. Patients were examined using echocardiography and USCOM at the following time points: Prior to the first anthracycline dose (T0), 6 h post infusion (T1), after 1 day (T2), after 7 days (T3), and after 3 months (T4), with CW-Doppler ultrasound (T0–T4) and echocardiography (only 2 measurements on T1, T4).

The evaluation of hemodynamic parameters included heart rate (HR), stroke volume (SV, by USCOM), cardiac output (CO; CO = HR × SV), and EF (by echocardiography). Serum biomarkers NT-pro-BNP and hs-Troponin T were determined at all time points (T0–T4). Drug administration, KPS, and toxicity or adverse events were recorded during the study period.

USCOM

The USCOM device provides a non-invasive bedside method to evaluate CO based on CW-Doppler ultrasound. After starting the USCOM device and before typing in the patients data (e.g. height, weight and gender), the left-sided transaortic (CO_{US-A}) or right-sided transpulmonary access (CO_{US-P}) has to be chosen. The flow profile is obtained using a 2.2-MHz transducer placed on the chest in either the left parasternal position to measure transpulmonary blood flow (right-sided access, 3rd to 5th parasternal intercostal space) or the suprasternal position to measure transaortic blood flow (left-sided access, suprasternal notch). The Doppler flow curve with maximal blood flow is recorded, which is characterized by a sharp, well-defined waveform with the clearest audible sound. The flow profile is displayed as a time-velocity curve on the monitor (VTI = velocity time integral). The device calculates CO as the product of SV and HR, where the SV is the product of the VTI and the cross-sectional area of the chosen valve (CSA). The chosen-valve CSA is given by the USCOM internal algorithm based on the typed-in patient data (height and gender).

Measurements made with the USCOM were taken while patients were hemodynamically stable (horizontal or sitting position). To exclude

inter-individual observer variability, all measurements by USCOM were undertaken by the same investigator.

Validation and reliability studies for USCOM have already been carried out in intensive care studies against invasive thermodilution (pulmonary artery catheter, and/or pulse-induced contour CO) with proven high correlation and limits of agreement according to Bland-Altman analysis [25–27].

Results

Patient Characteristics

Fifty patients (26 male, 24 female) with a median age of 59 years and a median KPS of 100% were included in the trial. Of the patients, 18 had a history of hypertension (36%), and 1 had a history of asymptomatic cardiac insufficiency (NYHA stage I, 2%). Patients were suffering from different types of cancer: 22 with lymphomas (44%), 17 with soft-tissue sarcomas (34%), 9 with acute myeloid leukemias (18%), and 2 with solid tumors (4%).

All patients received a first-line anthracycline-containing regimen for the malignant disease. The majority (n = 40, 80%) received doxorubicin at a median dose of 200 mg/m^2 (50–450 mg/m^2). 8 patients (16%) received mitoxantrone (which has a structural affinity to the anthracyclines), of whom 6 (12%) additionally received the anthracycline daunorubicin. The median cumulative doses were calculated at T4 (after 3 months). Detailed information is given in table 1.

Table 1. Baseline characteristics

	Median (range)	n	%
Gender			
Male		26	52
Female		24	48
Age	59		
KPS	100		
Pre-existing cardiovascular disease			
Hypertension		18	36
Heart insufficiency (NYHA I)		1	2
Cancer type			
Lymphoma		22	44
Sarcoma		17	34
AML		9	18
Solid tumor		2	4
Anthracycline-based treatment (cumulative dose at T4), mg/m^2			
Doxorubicin	200 (50–450)	40	80
Liposomal doxorubicin	175	1	2
Liposomal daunorubicin	120	1	2
Mitoxantrone	45 (40–50)	2	4
Mitoxantrone + daunorubicin	40 (30–50) + 180	6	12

KPS = Karnofsky-Performance Status; AML = acute myeloid leukemia; NYHA = New York Heart Association.

Hemodynamic Parameters

The initial value of the EF determined by echocardiography was 71 ± 7.8% (T0). After 3 months (T4) the EF decreased to 69.5 ± 7% resulting in a relative decrease of –2.1% (ΔT0–T4, p = 0.04). The corresponding values of the SV using CW-Doppler ultrasound were 54 ± 19.2 ml (T0), and 50.5 ± 20.6 ml (T4). The relative decrease of SV by CW-Doppler ultrasound was –6.5% (ΔT0–T4, p = 0.14). A summary of all parameters and values is given in table 2.

None of the patients developed symptoms for cardiac failure during the study period. Among the whole study population, 11 patients (22%) developed a clinically significant decrease of >10% in EF by echocardiography during the study interval (median EF $\Delta_{T0–T4}$ –14.1%, p < 0.001). Except for one patient (technical fault with the USCOM device), all of those patients showed a corresponding decrease of the SV by USCOM (median SV $\Delta_{T0–T4}$ –16.8%, p = 0.03) (fig. 1).

Kinetics of Hemodynamic Parameters and Serum Biomarkers

During the observation period an increase of serum biomarkers was observed. The relative increase of NT-pro-BNP was +28.9%, ΔT0–T4 (T0 229.2 ± 886.1 pg/ml, T4 295.4 ± 1161 pg/ml, p = 0.04). The corresponding values for hs-Troponin T levels were +51.9%, ΔT0–T4 (T0 7.7 ± 11.5 pg/ml, T4 11.7 ± 20.5 pg/ml, p = 0.001) (table 2).

Comparing the kinetics of biomarkers and hemodynamic parameters of 'non-high-risk' patients to those of 'high-risk' patients (as defined above; EF decreases by echocardiography >10%, ΔT0–T4), two striking differences were seen (fig. 2a, b):

– SV by USCOM decreased by 1 ml (ΔT0–T4) in 'low-risk' patients and by 10.5 ml (ΔT0–T4) in 'high-risk' patients.

Table 2. Medians (± SD) of parameters of echocardiography, USCOM and serum biomarkers during the study period (T0–T4)

	T0	T1	T2	T3	T4	ΔT0–T4, %	p[a]
Echocardiography							
EF ± SD, %	71 ± 7.8	–	–	–	69.5 ± 6.95	–2.1	0.04
USCOM							
SV ± SD, ml	54 ± 19.2	62.5 ± 23.4	61.0 ± 20.3	54.0 ± 22.5	50.5 ± 20.6	–6.5	0.14
HR ± SD, bpm	73 ± 14.1	74.5 ± 18.3	74 ± 18.5	76 ± 23.8	79.5 ± 13.7	+8.9	0.02
CO ± SD, l/min	4.2 ± 1.5	4.7 ± 2.0	4.2 ± 1.8	4.3 ± 1.8	4.35 ± 1.5	+3.6	0.46
NT-pro-BNP ± SD, pg/ml	229 ± 886	388 ± 1443	418 ± 1866	307 ± 1368	295.4 ± 1161	+28.9	0.04
hs-Troponin T ± SD, pg/ml	7.7 ± 11.5	7.1 ± 10.6	8.9 ± 11	8.9 ± 13	11.7 ± 20.5	+51.9	0.001

EF = ejection fraction; SD = standard deviation; SV= stroke volume; HR = heart rate; CO = cardiac output; [a]t-test.

– NT-pro-BNP levels in 'high-risk' patients increased by 254% (ΔT0–T2) within the first week compared to a more moderate increase of 185% (ΔT0–T2) within in the 'low-risk' patients (p = 0.04).

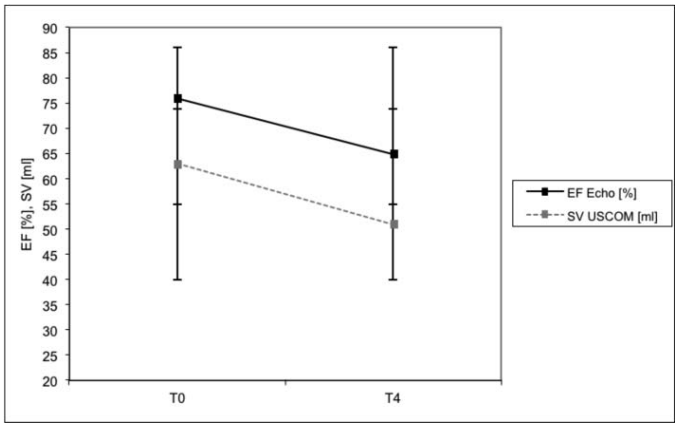

Fig. 1. Patients with an EF decrease of >10% (ΔT0–T4) by echocardiography (n = 11, median EF Δ_{T0-T4} –14.1%, p < 0.001); correlation to SV measurements by USCOM (ΔT0–T4) within this subgroup (n = 10, median SV Δ_{T0-T4} –16.8%, p = 0.03).

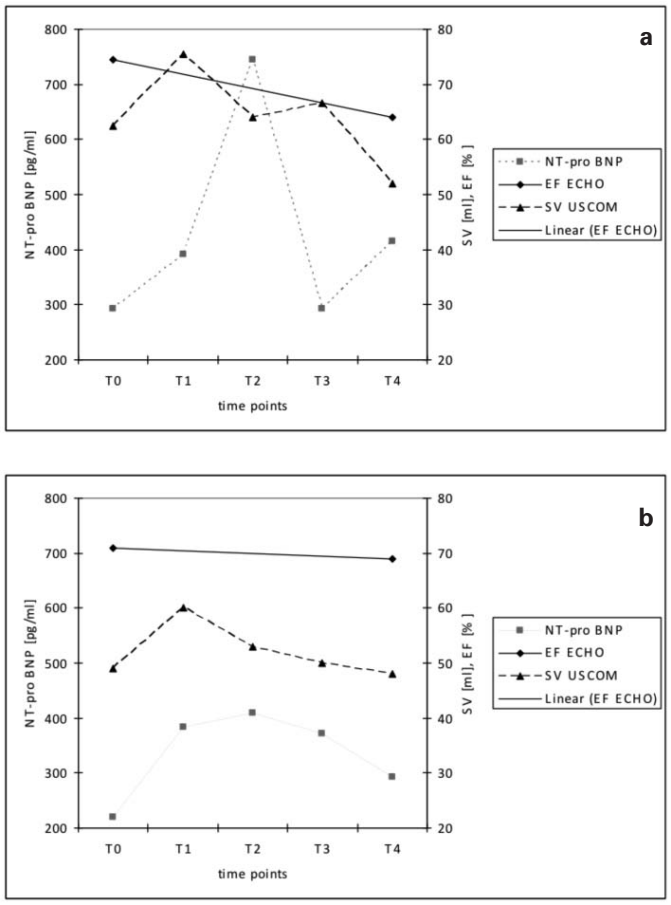

Fig. 2. Median of serum NT-pro-BNP kinetic and SV_{USCOM} (T0–T4) and $EF_{echocardiography}$ (T0, T4) in, **a** high-risk patients (EF decrease >10% ΔT0–T4), **b** non-high-risk patients.

Discussion

With the rapidly increasing arsenal of anti-tumor agents, the myocardial surveillance of patients who receive a potentially cardiotoxic agent is currently gaining in importance. The intention of routine cardiac monitoring is the early detection of restricted cardiac function, which would necessitate dose reduction or interruption (and/or application of cardioprotectants).

Cardiac function has to be monitored for years after anticancer treatment because of the possibility of a late-onset cardiotoxicity [28, 29]. Echocardiography is widely established, generally recommended and must be called the gold standard in clinical routine [7, 8]. Until now, all methods of myocardial monitoring and the recommendations have been validated solely for the anthracycline- and trastuzumab-induced cardiac damage.

USCOM is a non-invasive CO monitor based on the transthoracic measurement of Doppler flow velocity over the aortic and pulmonary outflow tract. It is easy to operate, and hemodynamic parameters are displayed 'beat by beat'. Following a short booting time the device can be used immediately. Moreover, the technique is reported to be easy to use after a short teaching period [30, 31]. Validation and reliability studies have been carried out in intensive care studies against invasive hemodynamic monitoring devices such as pulmonary artery catheter and other thermodilution techniques with proven high correlation [25–27].

Knobloch and co-workers used CW-Doppler USCOM and NT-pro-BNP measurements for monitoring the hemodynamic response in patients receiving an anthracycline- or trastuzumab-based regimen for breast cancer [23, 24]. In contrast to our study, their measurements were restricted to a short interval comprising the time prior to infusion until 10 min after infusion [23, 24]. In both studies, they demonstrated an immediate up-regulation of SV (and consecutively CO), suggesting that a compensatory hemodynamic mechanism might be involved [23, 24]. A volume effect could be ruled out since Knobloch et al. applied liposomal doxorubicin (equal infusion volume) to a comparative cohort in whom changes of SV or CO were not detected.

The finding of an increased SV (and CO) immediately after infusion was also seen in our study. Overall, SV increased from 54 ± 19.2 ml (T0) to 62.5 ± 23.4 ml (T1) and CO from 4.2 ± 1.5 l/min (T0) to 4.7 ± 2.0 l/min (T1), which was not related to an increasing heart rate (T0 73 ± 14.1 bpm, T1 74.5 ± 18.3 bpm).

Gustafsson and co-workers investigated the diagnostic and prognostic performance of NT-pro-BNP in primary care patients with suspected congestive heart failure. In summary, the mortality rate was higher in patients with NT-pro-BNP levels >125 pg/ml than in patients with normal values (p < 0.002). This difference persisted after controlling for age, gender, and LVEF [16]. Knobloch et al. observed an up-regu-

lation of SV that was more pronounced in patients with high NT-pro-BNP levels (>125 pg/ml) prior to the anthracycline infusion. They concluded that this finding might reflect a disturbed cardiac function even at baseline [23, 24].

In contrast to these reported trials, our study focused on the kinetics of hemodynamic parameters and biomarkers over a period of 3 months. Moreover, all recruited patients were chemo-naïve and had received a first-line anthracycline-containing regimen. The correlation of USCOM to the gold standard 'echocardiography' was evident in our trial. All patients (except 1 due to a technical fault of the USCOM device) who had developed a decrease in the EF detected by echocardiography during the study interval showed a corresponding decrease of the SV detected by USCOM. In addition to a more long-term effect, from the analysis of the kinetics of serum NT-pro-BNP levels in our patients, it can be hypothesized that there is also an 'immediate effect' of the anthracyclines. Not only was the increase of serum biomarkers inversely correlated to the EF by echocardiography and SV by USCOM, there was also an obvious striking increase of NT-pro-BNP levels following the anthracycline infusion, which was pronounced in 'high-risk' patients, defined as patients whose EF by echocardiography decreased >10% during the observation period (ΔT0–T4). The SV by USCOM decreased by 10.5 ml (ΔT0–T4), which was significantly different to 'low-risk patients' whose SV by USCOM decreased by no more than 1 ml during the study period (ΔT0–T4). Moreover, NT-pro-BNP levels in 'high-risk' patients increased by 254% (ΔT0–T2) within the first week compared to a more moderate increase of 185% (ΔT0–T2) in the 'low-risk' patients ($p = 0.04$). It may be possible that 'high-risk' patients could be identified by the early increase of NT-pro-BNP within the first week of treatment.

Despite some striking observations, the results and conclusions of our study are hampered by several factors:

1. The present study was initiated as a pilot study with the aim of evaluating the hemodynamic response to the anthracyclines with real-time CW-Doppler USCOM, echocardiography and serum biomarkers over a period of 3 months. It is not possible to draw any final conclusions from such a small study. Nevertheless, the study provides data justifying further clinical studies evaluating USCOM in hematology and oncology.
2. None of the patients became symptomatic for cardiac failure during the study period. Despite some significant changes in SV, EF and serum biomarkers, these observations were made in an asymptomatic patient population over a short interval of only 3 months. Moreover, the cumulative anthracycline doses were relatively low.
3. The accuracy of the USCOM depends on a good flow signal. Moreover, USCOM, like echocardiography, is an ultrasound-based device. For USCOM it has been shown that personnel can be trained to obtain reliable SV and CO estimations over the course of 20 patient assessments [30].
4. Biomarkers such as NT-pro-BNP are influenced by age, gender, renal function and co-medication with ACE inhibitors, β-blockers and diuretics. To our best knowledge, none of the patients included in the study had received such medications, and all had a serum creatinine level within the normal range.

In summary, the major findings of this study were: None of the patients became symptomatic for cardiac failure during the study period. A clinically significant decrease in the EF by echocardiography was mostly paralleled by a corresponding decrease in the SV by USCOM. The increase in levels of serum biomarkers was inversely correlated to EF by echocardiography and SV by USCOM, indicating a negative impact on myocardial function of the applied chemotherapy. Clearly, USCOM does not replace standard methods such as echocardiography in the cardiac surveillance of patients undergoing an anthracycline-based chemotherapy. But USCOM is attractive in many ways. It is easy to use, and as an ultrasound technique safe, so it can be used repeatedly to measure the trend over time. Moreover, using the USCOM device, the physician will obtain a result in an unbeatable period of time. The role of USCOM is evolving in intensive care medicine. In our opinion this technique deserves closer attention in the cardiac monitoring of cancer patient populations. The present study justifies further clinical studies evaluating USCOM in hematology and oncology.

Disclosure Statement

The authors declare no conflict of interest.

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