

Equilibrium radionuclide ventriculography: still a clinically useful method for the assessment of cardiac function?

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Abstract

The non-invasive assessment of left ventricular function with simple indices, such as left ventricular volumes and ejection fraction (LVEF), offers significant diagnostic and prognostic implications in the entire spectrum of cardiac diseases. Equilibrium radionuclide ventriculography (RNV) is a well validated technique for this purpose. Based on the principle that the amount of radioactivity emitted by technetium-99m (^{99m}Tc)-pertechnetate labeled erythrocytes in the cardiac chambers is proportional to the amount of blood contained, reproducible and accurate LVEF measurements can be obtained, with practically no geometric assumptions regarding heart shape. However, the development of other imaging techniques, mostly echocardiography and secondarily cardiac magnetic resonance has led to a decline in the use of RNV. This is due to easiness, cost and availability issues and also because competitive modalities can offer reliable anatomic and functional information and hence they can address a variety of clinical scenarios in one session. Nevertheless, RNV still remains a reliable method in clinical conditions, in which the detection of small changes in LVEF may be important in clinical decision-making, such as in patients undergoing cardiotoxic chemotherapy, when the images of different methods are of suboptimal quality or unobtainable, or there is discordance between clinical judgment and imaging results. In this respect the more recently introduced gated single photon emission tomography (SPET) myocardial perfusion imaging has not demonstrated equivalent reliability, in terms of independence from a variety of factors and accuracy of measurements on a per-patient basis. The purpose of this review is to present the features of RNV, and to define its role in the evaluation of cardiac function in the current era of medical imaging.

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Introduction

The assessment of left ventricular (LV) cardiac function and volumes is particularly important in patients with cardiovascular disease, since it provides significant diagnostic and prognostic information, which, in turn, may affect therapeutic decisions [1-3]. Several parameters have been proposed for the evaluation of LV systolic and diastolic performance. These indices can be obtained by invasive and non-invasive techniques. Indisputably, invasively derived parameters, such as maximal elastance and tau (τ) index, are the most accurate methods of assessing systolic and diastolic cardiac function, respectively [4]. However, the need for catheterization renders them impractical and not easily applicable in everyday practice. Therefore, noninvasive methods have been developed for the assessment of LV function. Both echocardiography and planar equilibrium radionuclide ventriculography (RNV) have been used for many years for this purpose and a wealth of data together with experience has been accumulated [5,6]. Cardiac magnetic resonance (CMR) has also evolved for assessing cardiac function but because of availability, technical restrictions and cost issues, this technique is confined in specialized centers. Gated single photon emission tomography myocardial perfusion imaging (SPET MPI) is also widely used. Among the systolic parameters, left ventricular ejection fraction (LVEF) is most extensively used to describe LV systolic performance, although it carries the disadvantages of being dependent on loading conditions and heart rate. Filling patterns of LV have also been evaluated by the above-mentioned techniques.

Regarding RNV, the vast majority of published research concerns the traditional planar (two-dimensional) technique rather than the tomographic one. The aim of this review is to put forward the most recent data concerning both planar and tomographic RNV in relation to other competitive methods in the contemporary clinical practice. The technique and certain parameters obtained are described in brief and the usual clinical applications of the method are reviewed.

Background, definition and principles of planar RNV

Planar RNV is performed by labeling patients' red blood cells (RBC) with the radioactive tracer technetium-99m (^{99m}Tc)-pertechnetate (usual adult dose 740MBq) which allows cardiac blood pool to be assessed with a standard gamma camera. As the amount of radioactivity within the cardiac chambers is very small, counts must be collected over few hundred cardiac cycles to obtain usable information. However, simply recording these counts would result in a blurred image because of cardiac wall motion. Hence, the cardiac cycle is divided into short intervals and separate images are acquired for each interval for a suitable length of time (typically 24-32 frames per cardiac cycle) (Figure 1). For this purpose the acquisition is gated to the patient's electrocardiogram (ECG) and the R wave indicates the start of a cardiac cycle. The frames correspond to different portions of the cardiac cycle and when sufficient counts have been collected in each one of them, they give the illusion of a beating heart if viewed in cinematic display on the computer. Since the amount of radioactivity in each chamber is proportional to the blood volume contained, the following variables can be assessed: morphology, quantitative indices of systole and diastole and regional wall motion [7,8]. Extreme R-R variations or excessive premature ventricular contractions may hamper RNV; moreover, irregularly irregular heart rhythm, as in atrial fibrillation, may render acquisition problematic or impossible [9]. The LV is the most systematically studied heart chamber in RNV and is best separated from the RV in the left anterior oblique view (best septal view), which enables an accurate calculation of LVEF and other variables.

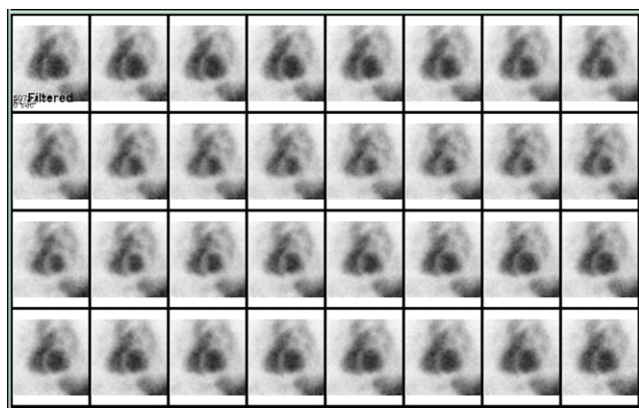


Figure 1. Successive radionuclide ventriculography images acquired in best septal view (typically 45° left anterior oblique) after labelling red blood cells with technetium-99m. The cardiac cycle was divided in 32 intervals (frames) and counts were collected in each frame over few hundred cardiac beats, gated with the electrocardiographic signal. The images were processed with a low pass filter (smoothed margins), which facilitates visual assessment in a cine-loop display of both the left and part of the right ventricle during systole and diastole.

Planar RNV is a simple and widely available method for non-invasively assessing LVEF, with a mid-range cost. The duration of the scan is usually 10-15 minutes for one projection.

Data analysis and interpretation

Qualitative evaluation

A complete planar RNV study includes the morphology and size of the LV as well as the measurement of the LVEF. Moreover, a fair idea of non-cardiac structures within the field of view, such as the great vessels and lungs, can also be obtained. In general, a normal ventricular size is expected in patients with normal ventricular contractility.

Qualitative evaluation

Left ventricular time-activity curve (TAC): LVEF, defined as the fraction of the LV end-diastolic volume ejected during contraction, is the most important index in a RNV study and is calculated by drawing a region of interest (ROI) around the LV. The major advantage of planar RNV is that EF measurement is practically independent of ventricular geometry. Left ventricular EF (normal values 50%-75%) equals the background subtracted counts in the end-diastolic frame minus the background subtracted counts in the end-systolic frame divided by the background subtracted counts in end-diastole. The LV TAC starts at end-diastole (maximum counts) and descends to the point of end-systole (minimum counts). With the onset of filling, the curve demonstrates an ascending, diastolic upslope in which some important phases of diastole are illustrated, such as the point of peak filling rate, the diastasis and the atrial filling phase ("atrial kick") (Figure 2). An absolute LV volume calculation, free of geometric assumptions, has been proposed and incorporated into guidelines [10].

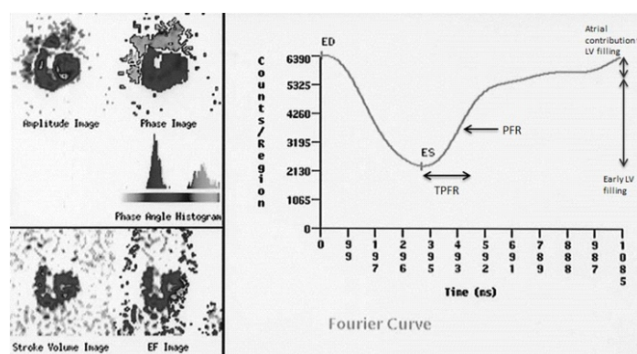


Figure 2. The left ventricular time-activity curve (volume curve) of a background corrected representative (average) cardiac cycle. The x-axis represents time length across an average cardiac cycle and the y-axis represents activity (counts) within the LV ROI. The diastolic function indices peak filling rate (PFR) and time to PFR (TPFR) are depicted. On the left side the Phase and Amplitude parametric images, together with the stroke volume (SV) (end-diastolic-ED counts minus end-systolic-ES counts per pixel) and EF (SV to end-diastolic volume per pixel) functional images are all coded on a grey-scale.

Diastolic performance: Diastolic dysfunction precedes systolic dysfunction [10,11]. Therefore, the study of diastole may be useful in the management of patients with coronary artery disease (CAD) and heart failure [12-14]. The most common diastolic indices calculated with planar RNV are the peak

filling rate (PFR), which represents the early rapid ventricular filling, and the time to PFR, which is the interval from the end-systole until PFR occurs [15-17]. Nevertheless, due to its limited temporal resolution, radiation exposure, cost, as well as the availability and easiness of echocardiography, planar RNV is not used nowadays to assess diastolic function alone [18]. Notably, however, planar RNV offers an assessment based on an average of several hundred cardiac cycles and relies on volume changes during diastolic filling, in contrast to maximal transmitral blood flow velocities obtained over few cardiac cycles in echocardiography.

Parametric analysis

Parametric images incorporate an analysis of the TAC in each pixel of the blood pool scintigraphy. The first harmonic Fourier transform is fitted in each pixel TAC, providing a cosine curve, which is characterized by its amplitude and the phase angle of the time point in which maximal amplitude is attained during the cardiac cycle. As such, the amplitude is the degree of regional change of counts on a per-pixel basis, which reflects volume displacement and hence the magnitude of contraction. The phase angle indicates the timing of contraction and it illustrates the propagation of mechanical activation, thus reflecting the sequence of contraction. This information is usually color or grey-scale coded with reference to maximal amplitude or to phase angle to form a functional image of such data, namely the amplitude and phase images (Figure 2). In particular, phase images may be useful in diagnosing dyssynchrony; in cases of conduction disorders, such as bundle branch blocks, or LV aneurysms, phase images will illustrate the affected areas as 'out of phase' to adjacent LV portions due to premature or delayed contraction [9,19].

Tomographic equilibrium radionuclide ventriculography

Echocardiography-gated blood pool SPET allows for better separation of the cardiac cavities and hence it can overcome the problem of the overlapping chambers with planar RNV, which is particularly important in the evaluation of RV function [20]. In addition, tomographic RNV may facilitate a thorough assessment of regional wall motion. Notably, LVEF measurements with SPET RNV are considerably higher than those calculated with planar RNV [21]. A good correlation was found between SPET RNV and CMR but the 95% limits of agreement were wide [22,23]. Moreover, the results of LV volumes and EF measurements, although reproducible, can have significant variations as they depend highly on the software package and are imprecise in distorted cavity geometry [22, 23]. Therefore, since planar RNV offers accurate and precise LVEF measurements and is simple and widely validated, it is preferred over SPET RNV for routine clinical purposes. On the other hand, the tomographic acquisition may be selected for a reliable assessment of both LVEF and RVEF in a single examination. Interestingly, the recently introduced dedicated cardiac SPET cameras, equipped with cadmium-zinc-telluride crystals, lead to increased efficacy along with shortened acquisition times or reduced radiation doses to the patients, when compared to conven-

tional SPET cameras [24]. In a recent publication it was shown that the improved count sensitivity achieved with the use of high-efficiency SPET systems can reduce injected activity by 50% while maintaining short imaging times of 5 minutes [25].

Clinical applications

According to the appropriate use criteria concerning cardiac radionuclide imaging of the American College of Cardiology Foundation (ACCF), planar RNV is a generally acceptable and reasonable approach for the assessment of LV function in the absence of a recent reliable diagnostic information regarding ventricular function obtained with another imaging modality and also for assessing potentially cardiotoxic therapy (e.g. by doxorubicin) [26].

Moreover, according to the guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) (2003) and the European Association of Nuclear Medicine (EANM)/European Society of Cardiology (ESC) guidelines for radionuclide imaging of cardiac function (2008), planar RNV can be used in several clinical scenarios, such as the assessment of LV function after an acute ST-elevation myocardial infarction (STEMI), or non-ST-elevation myocardial infarction (NSTEMI) and unstable angina, and also LVEF monitoring in aortic regurgitation [6,27]. Despite these recommendations, the clinical use of RNV currently is restricted mainly in monitoring the LVEF in patients receiving cardiotoxic chemotherapeutic drugs.

Chemotherapy cardiotoxicity monitoring

It is well documented that certain chemotherapeutic agents, such as anthracyclines (for example doxorubicin and epirubicin), commonly used in the treatment of childhood acute lymphoblastic leukemia, lymphoma and breast cancer and also trastuzumab (herceptin), a monoclonal antibody directed against the HER 2 receptor used for treatment of breast cancer, demonstrate cardiotoxic effects, potentially resulting in progressive heart failure [28-30]. Due to variations in susceptibility there is no particular threshold for myocardial damage, although cumulative anthracycline exposure is a consistent risk factor, and the standard method to detect chemotherapy-induced cardiotoxicity is serial LVEF measurements [31].

Although echocardiography is the most widely accepted method of monitoring LVEF during chemotherapy, planar RNV may play a significant role. In adults, in particular, serial RNV is considered the optimal method, since it is a very accurate, reproducible, and cost-effective noninvasive method of detecting small changes in LVEF [26, 27, 29, 32-36]. Nouisainen et al. (2001) using both RNV and echocardiography studied prospectively a group of adult patients who received doxorubicin to a cumulative dose of 400-500 mg/m². Despite a reasonably good correlation between these techniques in the determination of LV systolic function, their agreement was unsatisfactory. Moreover, echocardiography was limited by a significant intra- and interobserver variability. Based on these results, the authors concluded that RNV should be preferred over echocardiography in ad-

ult lymphoma patients during anthracycline chemotherapy [37]. This research group went on and compared prospectively planar RNV and CMR in cardiac monitoring during doxorubicin-based chemotherapy in adult patients suffering from non-Hodgkin lymphoma. Planar RNV was found to be more sensitive in detecting clinically important LVEF reduction during treatment, thus proving its role as a valuable tool in identifying early, subclinical deterioration of cardiac function [38].

In pediatric patients echocardiography is the method recommended for serial assessment of LV function, due to lack of ionizing radiation, portability and availability [39]. Interestingly, in a study by Tantawy et al. (2011) involving 39 children with Hodgkin lymphoma receiving doxorubicin, planar RNV was more sensitive than echocardiography in detecting early impairment of LV function [40]. Basar et al. (2014) studied 56 childhood cancer survivors for the evaluation of anthracycline-induced chronic cardiotoxicity and found that similar EF values were obtained by CMR and planar RNV, and those values were significantly lower than the echocardiography measurements. Among patients with pathologic findings in at least one of the 3 techniques ($n=20$) one patient diagnosed with systolic dysfunction and four patients diagnosed with both systolic and diastolic dysfunction by RNV, had normal findings on echocardiography and CMR. Moreover, three patients with abnormal LV wall motion detected by CMR had normal findings with the other tests. The authors concluded that in the long term, patients must be scanned by echocardiography every two years, due to its wide availability and low cost, but CMR and planar RNV can detect subclinical cardiotoxicity more reliably in patients treated with high-dose anthracycline therapy (cumulative doses of more than $200\text{mg}/\text{m}^2$) [41].

The clinician should bear in mind that individualization of antineoplastic/anthracycline therapy ideally should begin with a pre-treatment baseline determination of LVEF to detect pre-existing heart disease. There are no widely accepted guidelines for cardiac monitoring of patients receiving anthracyclines. The American Society of Clinical Oncology recommends (1) evaluation of LVEF: a) Prior to each course of doxorubicin, b) After a cumulative dose of $400\text{mg}/\text{m}^2$ is reached, c) A repeat assessment after a cumulative dose of $500\text{mg}/\text{m}^2$ and d) Thereafter, assessment after every $50\text{mg}/\text{m}^2$ of dose escalation [42]. Chemotherapy should be stopped if there is an indication of cardiotoxicity suggested by a $>10\%$ decrease in LVEF to $<50\%$, if there is an absolute decrease in LVEF $\geq 30\%$ or if the final LVEF drops to $\leq 30\%$ [9]. Regarding the imaging modality applied, it has been proposed an echocardiography to be performed before every course of doxorubicin up to a total dose of $300\text{mg}/\text{m}^2$ [40]. Planar RNV should be performed if the patient is receiving more than $400\text{mg}/\text{m}^2$ of the drug in one course. Echocardiographic evaluation should be repeated 3, 6, and 12 months after the completion of therapy and every 2 years thereafter, whereas RNV should be performed after 12 months and then every 5 years. However, RNV remains one of the most widely methods for reliable LVEF measurements [35].

Assessment of cardiac mechanical dyssynchrony

Cardiac resynchronization therapy (CRT) has emerged as an

effective treatment option in heart failure refractory to medications [43]. Cardiac resynchronization therapy is recommended in end-stage heart failure patients (NYHA class II-IV) who have a reduced LVEF ($\leq 35\%$) and a prolonged QRS complex ($\geq 150\text{msec}$), which is considered to reflect inter-ventricular delay [44]. However, approximately 30% of patients are non-responders to CRT [45]. Given the high cost and complications related to CRT, it is clear that a reliable selection of patients who would mostly benefit from this treatment is of paramount importance.

Mechanical dyssynchrony has been recognized also as a prognostic factor of response to CRT [46]. Due to the fact that QRS duration is a measure of electrical but not mechanical delay, a variety of imaging techniques, have been proposed for the evaluation of mechanical dyssynchrony and identification of potential responders to CRT [47]. The utility of planar RNV and in particular of phase analysis, to reliably assess mechanical dyssynchrony has been highlighted in several studies [48-51]. In a recent prospective study including 32 non-ischemic dilated cardiomyopathy patients undergoing CRT implantation it was shown that certain variables derived from RNV phase analysis were univariate predictors of response to treatment, while QRS duration was not a determinant of response [52]. In line with these findings were the results of a retrospective study published in the same year, which was performed in a cohort of 146 ischemic and non-ischemic heart failure patients. Using phase analysis, the authors showed that the RNV mechanical dyssynchrony pattern was linked to the underlying cardiomyopathy and it was not necessarily associated with electrical dyssynchrony; moreover, the comparison of survival between CRT and non-CRT patients according to dyssynchrony status revealed no difference in patients with no RNV dyssynchrony while a significant difference was observed in patients with a high level of mechanical dyssynchrony [53]. These results suggest that planar RNV may be helpful in the prediction of response to CRT.

Other applications

Radionuclide ventriculography has been used in the past in several other clinical scenarios, such as the prognosis and assessment of therapy after MI, the diagnosis and management of patients with known or suspected chronic CAD and the assessment of LV function in patients with heart failure. Nowadays, however, this modality is rarely (if at all) used for these indications, since alternative methods are preferred, more commonly echocardiography.

Although very seldom and selectively applied, planar RNV is assigned a class I/IIa indication for the assessment of resting RV function after suspected RV infarction, in arrhythmogenic RV dysplasia and in monitoring valvular and congenital heart disease and also in cardiac transplant recipients [28,54].

Comparison of planar RNV with other techniques

The accuracy of planar RNV in the determination of LVEF was demonstrated in comparison with contrast angiography [55, 56]. Moreover, its high reproducibility has been

supported by several studies [37, 55, 57-60]. Nevertheless, currently two-dimensional (2D) echocardiography is the most widely used technique for the assessment of LV volumes and EF. The widespread availability, lack of ionizing radiation, ease of performance, even at patient's bedside, and low cost are the most important advantages of echocardiography. Furthermore, with the introduction of contrast agents echocardiography is very efficacious in assessing global and regional wall motion abnormalities, even in cases with suboptimal image quality and very rarely another technique is used for this purpose [61]. This modality is recommended for first-line testing of cardiac function in clinical guidelines [62-64]. The agreement of LVEF measurements between planar RNV and 2D echocardiography is good, but RNV tends to show a higher reproducibility [38, 59, 60, 65, 66]. The main disadvantage of 2D echocardiography is that it relies on geometrical assumptions for the estimation of LVEF, unlike RNV. Three-dimensional (3D) echocardiography is devoid of this limitation and appears to be more accurate and reproducible than 2D echocardiography for the measurement of LV volumes and EF but because of its lower temporal and spatial resolution compared to 2D echocardiography, it results in more patients as having non-high quality images [67]. Three-dimensional echocardiography has been shown to correlate well with planar RNV for LVEF calculation [68-70]. However, there are few cases such as very thin or obese patients, patients with emphysema, breast implants, patients with distorted LV geometry due to infarction or cardiomyopathy where satisfactory LV images cannot be obtained, even with the use of contrast agents. This is the subset of patients that could derive the greatest benefit from assessment of LVEF by RNV.

Cardiac magnetic resonance (CMR) provides an accurate and highly reproducible assessment of cardiac volumes and function, and is currently considered the gold standard for the assessment of both LV and RV volumes and EF [71]. Cardiac magnetic resonance has similar temporal resolution to planar RNV, is radiation free, yet not necessarily risk free [72, 73]. Nevertheless, not all patients are suitable for a CMR examination, e.g. patients with non-magnetic resonance imaging (MRI) safe pacemaker or claustrophobia. Moreover, MR scanners are not widely available, the technique has a high cost, and it requires significant expertise limiting its routine application in a fraction of patients [74]. In addition, there are significant difficulties in performing CMR in patients with arrhythmias (e.g. atrial fibrillation), whereas a reliable assessment of the diastolic function remains an elusive task. In a comparative study, a good agreement and similar limits or reproducibility were found between planar RNV and CMR for assessing the function of the systemic right ventricle in patients submitted to surgical repair for transposition of great vessels, suggesting that planar RNV may be an equivalent alternative in cases that CMR imaging is not available or appropriate [75].

Gated SPET MPI is a widely used technique, which is endorsed by international guidelines [6, 26]. It can provide useful information on LVEF, wall motion and wall thickening together with perfusion data simultaneously in a single acquisition [76, 77]. However, gated SPET MPI is hampered by a limited temporal resolution and for example LVEF measu-

rements are systematically lower when 8 frames per cardiac cycle are used in comparison to 16 frames [78, 79]. Moreover, the assessment of diastolic function may be problematic, unlike planar RNV [6]. Furthermore, deviations in LVEF measurements between different software packages can be significant [80, 81]. This is due to the fact that the gated SPET LVEF calculations rely on volume measurements based on the determination of the wall borders at end diastole and end systole [6]. In addition, LVEF can be overestimated in patients with small LV cavities, as in women, due to an end-systolic volume (ESV) underestimation. This is caused by blurring of the LV cavity border secondary to the relatively limited resolution of the gamma camera compared with wall thickness and the additive effect of an increase in myocardial count density during contraction [82]. An underestimation of gated SPET MPI LVEF may occur also in cases with severe perfusion defects [83]. A gated SPET MPI LVEF calculation is not recommended in patients with arrhythmia, even in those with atrial fibrillation or frequent premature ectopic beats [82]. In our experience this is feasible with planar RNV by a prolongation of the acquisition time to account for counts losses of the rejected beats.

A major limitation in the clinical application of gated SPET MPI is the inaccuracy in measuring volumes and LVEF on a per-patient basis. Inconsistencies in the agreement between methods, despite a good correlation, have been demonstrated earlier in comparison to both CMR and planar RNV by our team and other authors [84-88]. A recent multicenter study also has shown a substantial variation between echocardiography, CMR and gated SPET MPI in LVEF determination, hence highlighting the limitations in the interchangeability between those methods [84]. It should be realized that guidelines support the use of gated SPET together with perfusion assessment as a diagnostic aid and a prognostic variable. However, this technique is not specified in the recent clinical guidelines for an isolated and reliable assessment of LVEF [62-64].

Overall, concerning the measurement of LVEF, planar RNV has the least operator dependence and variability compared to both echocardiography and gated SPET MPI [89, 90] and is likely that it offers an assessment of similar reliability to that of CMR, in a simple and cost effective manner [38, 41, 75].

Is there a place for RNV in today's clinical practice?

Despite the advent of modern technologies in the assessment of LV function, planar RNV retains its strength over alternative methods for this type of evaluation. Planar RNV is practically independent from the operator's experience and patient's habitus, its performance is not hampered by cardiovascular implantable electronic devices, and it may offer precise and accurate measurements of the LVEF. This is particularly desirable in clinical conditions, in which the detection of small changes in EF may be important in clinical decision-making, such as in patients undergoing cardiotoxic chemotherapy and also when alternative imaging methods are of suboptimal quality or unobtainable, or there is discordance between clinical judgment and imaging results [91].

The authors declare that they have no conflicts of interest

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