Septal flash: At the heart of cardiac dyssynchrony

Simon Calle¹, Christophe Delens¹, Victor Kamoen, Jan De Pooter, Frank Timmermans(*)

Department of Cardiology, University Hospital Gent, Gent, Belgium

ARTICLE INFO

Keywords:
Cardiac dyssynchrony
Septal flash
Cardiac resynchronization therapy
Left bundle branch block

ABSTRACT

Cardiac resynchronization therapy (CRT) has been a major step in the treatment of heart failure patients and intraventricular conduction delay. As a considerable number of patients do not respond adequately to CRT, echocardiographic dyssynchrony selection criteria have been proposed to improve CRT response, but these parameters eventually failed to provide superior selection of CRT candidates.

In the last decade, an echo-dyssynchrony parameter called “septal flash” was reported by several investigators and opinion leaders in the field of CRT. This parameter has a strong pathophysiological rationale and was shown to be a robust and predominant predictor of CRT response in recent observational and retrospective studies. We here provide a comprehensive and balanced overview of septal flash and address several important aspects, questions and potential future implications of septal flash in cardiomyopathy and CRT.

© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. [http://creativecommons.org/licenses/by-nc-nd/4.0/]

Introduction

Cardiac resynchronization therapy (CRT) was conceived to target heart failure patients with intraventricular conduction delay (wide QRS complex) that is associated with poor coordination of ventricular contraction and clinical outcome [1]. However, a considerable number of patients do not appear to respond adequately to CRT and attempts to predict and improve CRT response rates have focused on the presence and magnitude of cardiac dyssynchrony. Dyssynchrony has been assessed by a plethora of echocardiographic methods and appeared promising in initial monocenter studies [2,3]. The concept that echo-dyssynchrony provided superior patient selection compared to QRS duration/morphology also fueled interest for targeting dyssynchrony in heart failure patients with narrow QRS [4]. However, multicenter studies have cast serious doubts on the value of the echo-dyssynchrony parameters and therefore they have never been considered by international guidelines [5,6]. Also in narrow QRS, echo-assessed dyssynchrony seemed futile in most patients, and concerns were raised because of possible harm [4].

Why is there dyssynchrony?

The definition of dyssynchrony, its pathophysiology, and the way it should be captured/measured have been a matter of debate in the field of CRT for many years.

Mechanical dyssynchrony has been defined as the disparity in regional contraction timing or an uncoordinated, non-homogeneous regional myocardial contraction. This uncoordinated contraction has mostly been assessed by echocardiography [7]. However, most studies have examined wall motion with echocardiography, but the measurements did not clarify whether the cause of dyssynchrony is related to a delay in electrical activation (broad QRS) or results from heterogeneity in loading and/or contractile properties of the wall, independent of QRS duration. In essence, dyssynchrony can be triggered by (a) an electrical substrate (i.e., left bundle branch block, LBBB) that is potentially responsive to CRT and (b) pure mechanical dyssynchrony (e.g., heterogeneity in loading) that is not fed by an electrical substrate, and therefore less or unresponsive to CRT [8]. However, with the echocardiographic techniques used in the early CRT studies, it remained difficult to distinguish electrical from pure, primary mechanical dyssynchrony. This missing link between mechanical and electrical dyssynchrony likely explains part of the controversy on echo-dyssynchrony measures to improve patient selection and response to CRT.

* Corresponding author at: Department of Cardiology 8-K12, University Hospital Gent, C. Heymanslaan 10, Gent 9000, Belgium.
E-mail address: frank.timmermans@agent.be (F. Timmermans).
1 Both authors contributed equally.

https://doi.org/10.1016/j.tcm.2019.03.008
1050-1738/© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. [http://creativecommons.org/licenses/by-nc-nd/4.0/]

Please cite this article as: S. Calle, C. Delens and V. Kamoen et al., Septal flash: At the heart of cardiac dyssynchrony, Trends in Cardiovascular Medicine, https://doi.org/10.1016/j.tcm.2019.03.008
Fig. 1. Septal flash on M-mode imaging.
A parasternal M-mode of the LV is shown from a patient with typical LBBB, demonstrating septal flash (yellow arrows). A short inward motion of the septum (before ejection) is followed by stretching of the LV lateral wall. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Septal flash: The optimal marker of electro-mechanical dyssynchrony?

History of septal flash

Septal flash (SF) was described for the first time by Feigenbaum’s group in 1974 where “septal beak” was described with M-mode in patients with LBBB (Fig. 1) [9]. The prevalence of SF among LBBB patients varies substantially (45–63%), depending on the population studied and on how stringent LBBB criteria are applied [10,11]. Also, the temporal relationship between the occurrence of LBBB and SF is unknown, as no large epidemiological or follow-up studies are available on this issue [12]. Importantly, in the early years of “dyssynchrony in CRT”, many echo-dyssynchrony parameters have been reported, but septal beak or SF was never considered [5]. Only in 2008, Parsai et al. introduced this particular septal motion in the field of CRT as a specific marker of dyssynchrony due to electrical disease [13]. Eventually, the presence of SF was shown to be a robust and dominant predictor of CRT response in heart failure patients with LBBB in observational and retrospective studies [11,14–18].

Pathophysiology of SF

In Fig. 2, an echocardiographic speckle tracking-based strain analysis of the septal wall and postero-lateral wall is shown of a patient with LBBB and a clear SF [8,19,20]. As can be appreciated, SF makes part of a typical contraction-and-stretch pattern of the left ventricular (LV) wall in LBBB, as explained in the Fig. 1 legend. SF is a fast leftward septal motion during early systole, that starts and mostly ends before opening of the aortic valve; it thus occurs during most of the systolic isovolumetric period [8]. This SF movement can be easily seen with simple eye-ballling during echocardiography and can be captured on septal strain analysis as shown in Fig. 2 [11]. Although the main focus of this review is on SF, apical rocking (AR) also makes up part of the typical LBBB contraction pattern and both are therefore strongly interrelated [11]. During the SF right-to-left motion, the LV apex is tethered towards the septum, which constitutes the first part of the AR movement. At the time of SF and early AR, the postero-lateral wall is stretched, which is shown in Fig. 2. This postero-lateral pre-stretch is caused by the relative premature contraction of the right ventricle (RV) and septal wall [8,21–23]. Animal studies and simulation models have provided evidence that SF has both an active (septal contraction) and passive component. The passive component is due to the relative premature contraction of the RV compared to the LV that creates an early transseptal pressure difference between right and left ventricle, causing the septum to move from right to left [21–24]. In typical LBBB, the septum is electrically activated from the right side instead of the left side, and this right-to-left transseptal activation is significantly prolonged in LBBB [25,26]. Following this transseptal depolarization, the subendocardial septal LV region is reached at a septal breakthrough site, and impulse propagation ensues along the LV. However, electro-physiology (EP) studies in patients with LBBB and SF have described functional lines of conduction block that slow conduction
to the postero-lateral wall, and hence cause delayed contraction of the postero-lateral wall [26]. The pathophysiological mechanisms governing these functional lines of block remain unknown, but it is hypothesized that the premature RV contraction and SF itself may induce myocardial stretch that causes slowed conduction [26]. However, there is controversy on the occurrence of these “lines of block” in LBBB, and some authors even suggest that these lines of block represent artifacts [27–29]. Therefore further clarification is needed on this issue.

When the postero-lateral wall finally contracts, the septum is stretched from left to right (so-called septal rebound stretch, SRS (Fig. 2)) and the LV apex moves to the left, creating the second movement of the AR [21,24].

Thus, it can be appreciated that SF makes part of an LBBB-altered activation pattern with early RV and septal contraction relative to the postero-lateral wall. Secondly, SF and AR both reflect the same underlying pathophysiology and both are mostly present in the same patients, although sometimes with different magnitude [11]. As SF makes up part of the sequential events in the LBBB-induced dyssynchrony pattern, this makes it a robust and pathophysiological marker of true electrically-mediated dyssynchrony. As such, SF differs from previous echo-dyssynchrony approaches that only focused on time delays between myocardial segments and RV/LV ejection delays, and potentially captured “dyssynchrony” independent from an electrical substrate (“false positive”) [8]. Moreover, SF may not have been captured with previous echo approaches as these methods mainly focused on longitudinal motion, whereas SF is a predominant transversal motion [26]. Especially in systolic and diastolic heart failure, longitudinal LV shorting is first and mostly more affected than radial wall shortening [30]. Last but not least, time delays between contraction of myocardial segments have been considered within the LV ejection window and might not have captured true electro-mechanical dyssynchrony because SF occurs before ejection [8].

In CRT literature, terms such as SF, AR, SRS and systolic stretch index (SSI) are often used by investigators and this terminology may appear confusing for practitioners in the field. However, as shown in Fig. 2, these myocardial contraction-and-stretch indicators all make part of the typical LBBB contraction-and-stretch pattern of the septal and postero-lateral wall. SSI is defined as the sum of early postero-lateral prestretch and SRS (2 + 4). The LV pressure tracing reveals septal shortening during relatively low LV pressure. The x-axis denotes time whereas the y-axis provides strain values in %. MVC: mitral valve closure; AVO: aortic valve opening; AVC: aortic valve closure; MVO: mitral valve opening. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

How to assess SF?

SF has mostly been assessed by echocardiography using eyeballing, M-mode and speckle tracking-based strain imaging, as illustrated in Figs. 1 and 2, but also using magnetic resonance imaging [8,13,17]. The related AR movement is also easy to assess visually and the group from Voigt established an approach for quantifying AR [24].

A gold standard method for assessing the qualitative nature of SF in humans is lacking. Moreover, the extent of SF may vary from patient to patient and the assessment is affected by the investigator’s level of experience [10,33]. Therefore, some of the criticism on SF may relate to the eye-ballling method. However, eye-ballling is inherent to echocardiography and visual function assessment is not uncommon among experienced echocardiographers. Visual assess-
ments in echocardiography correlate well with formal methods of quantification and it is even the guideline-recommended method for decision-making in several fields (e.g. stress echocardiography) [11]. In this regard, De Boeck et al. invited 9 expert faculty members of an international echocardiography congress to analyze velocity traces from 18 consecutive patients. Full agreement occurred in only 3 cases, resulting in an interclass correlation coefficient of 0.42. In contrast, visual assessment of “dysynchrony” scored better than many of the echo-dysynchrony parameters at that time. However, it remains unknown whether the visual dys synchrony assessment involved SF in that study [34]. In studies assessing the presence of SF and AR, interobserver agreement for visual assessment of SF and AR in LBBB patients varied from 79% to 100% and from 86% to 88%, respectively [10,11,14,33].

In the literature, speckle tracking echocardiography has been used to assess LBBB contraction patterns in longitudinal, radial and circumferential directions. As SF is reported to be a predominant transversal motion at visual inspection, radial strain analysis would logically be a good approach to identify potential responders to CRT [36–38]. However, longitudinal strain analysis is mostly performed/reported, as it might be more feasible and reproducible than radial strain [31]. Moreover, in general longitudinal strain values correlate better with outcome compared to radial strain values [30]. More specifically, also longitudinal speckle tracking-assessed SRS and SSI predict reverse remodeling and improved outcome after CRT [31,32].

Does SF define typical (proximal) LBBB?

An EP study in LBBB patients has shown different electrical activation patterns with regard to transeptal conduction time, heterogeneous foci of septal breakthrough, and functional lines of block in the LV. Notably, these heterogeneous EP patterns could not be discerned by the surface ECG [25]. However, in this study, heterogeneous cardiac diseases were examined and this might explain the variable EP patterns [25]. On the contrary, in patients with LBBB and SF, a more consistent EP pattern was observed, indicating that SF probably identifies a particular subset of “LBBB hearts” [26]. Moreover, as experimental LBBB (ablation of the proximal part of the left bundle) generates a typical SF, it can be assumed that the EP pattern in these LBBB/SF patients is related to the proximal nature of the conduction block [22,39]. Aortic valve interventions can also cause LBBB, and the fact that His-bundle pacing can correct LBBB strongly argues for a proximal pathogenesis of LBBB [40]. Obviously, more studies are required to assess the relation between proximal LBBB genesis and SF.

Blunting, obscuring or mimicking SF: potential scenarios

It was previously shown that SF does not occur in patients with conduction blocks other than LBBB, such as right bundle branch block (RBBB), left anterior hemiblock or left posterior hemiblock [10]. Therefore, SF is an electro-mechanical dysynchronous marker that occurs specifically in patients with LBBB. Yet, several conditions that could obscure or prevent SF despite “typical LBBB” have been suggested and are listed in Table 1 [21,23,41].

For instance, coexisting myocardial disease/scar that affects regional contractility at the septum/lateral wall can modify the electro-mechanical sequences that govern SF [41,42]. In fact, a study by the Smiseth group induced LV lateral wall ischemia in dogs with experimentally induced LBBB and observed an abolished SRS, eventually masking SF and improving septal systolic shortening [43].

Also, pathologies that affect the RV or RBBB may affect the appearance or magnitude of SF [21,23]. In line with this, it can be hypothesized that for SF to occur, the conduction properties of the RBBB should be intact because slowed RBBB conduction could affect (a) the simultaneous “en masse” right-to-left septal activation (active component of SF) and (b) the RV contraction that governs the passive right-to-left component of SF.

Importantly, although the simulation studies by the Prinzen group provided some scenarios and insights on why SF might not occur [21], it remains unclear how the altered contractility simulations in their CircAdapt model would be compatible with true LBBB, which is the major target population in CRT. Indeed, some of the potential scenarios listed in Table 1 (d, e, g), such as a large septal scar etc., may not be compatible with a typical LBBB on the surface ECG.

Could we unmask SF in situations that blunt or obscure SF? The answer to this question remains unclear, and we can only encourage future investigations on this issue. Obviously, the surface ECG should always be carefully evaluated for the presence of typical LBBB, as SF occurs only in “bona fide” LBBB. Of interest, one study showed that a dobutamine challenge has the potential to unmask or increase SF [44].

Finally, some conditions could theoretically also mimic SF to some degree. Passive right-to-left lateral motion could occur in high RV pressures and/or septal scar. However, in these conditions, the right-to-left septal movement is not supposed to be as short-lived as SF, but it might be challenging for less trained echocardiographers.

LBBB-induced LV remodelling

Smiseth’s group has demonstrated that LBBB causes septal hypococontractility [45]. Since the septum represents approximately one third of the LV mass, loss of a large portion of septal contribution to LV function in LBBB adds substantial workload on the LV lateral wall. This loss of septal work and increased workload on the lateral wall is probably a major stimulus to adverse LV remodelling in patients with LBBB, and may be causative or contributive to further LV dysfunction. In other words, LBBB may be the primary cause of cardiomyopathy (CMP) (LBBB-induced CMP), but can as well contribute to further LV dysfunction in patients with a co-existent CMP unrelated to LBBB [46]. As LBBB acts directly on the LV ejection fraction, this may explain why some-stud-
ies have concluded that LBBB is not an independent cardiovascular risk factor, as correcting for ejection fraction eliminates the most important hemodynamic effect of LBBB [19]. Given the evidence that LBBB directly affects LV hemodynamics, it also has been questioned whether or to what extent heart failure medications could tackle this LBBB-related mechanical LV pathology [47].

As described earlier, LBBB hearts often reveal hypertrophy of the LV lateral wall and thinning of the septum [39]. The reason for the septal thinning is not entirely clear, but probably reflects a “muscular deconditioning or hibernation” as the septal contribution to LV ejection is excluded in typical LBBB/SF. Indeed, in typical LBBB patients with SF, septal contraction starts and ends in the systolic isovolumetric phase and therefore does not contribute to ejection of blood [8,39]. Therefore, the relatively early septal contraction in LBBB is adjudicated as “wasted energy” that is transferred to the stretching of the postero-lateral wall rather than its contribution to ejection of blood [45]. In line with this, the main reason for reduced septal perfusion in LBBB is probably normal autoregulation of the myocardial microcirculation and perfusion due to less septal metabolic demands [48]. Conversely, the compensatory work of the lateral wall, triggered by the early stretch due to “premature” RV and septal contraction induces the typical lateral hypertrophy [39].

In animal studies, the acute occurrence of SF after induced LBBB has been described [42,43,49]. In humans, there are currently no community data available on the natural history of SF following the onset of LBBB in humans. It therefore remains speculative whether SF is already present or prominent following acute LBBB, or whether it first requires a LBBB-induced LV remodelling to the “thin-septum-thick-lateral-wall” phenotype before SF emerges or becomes more prominent. A recent study investigated the occurrence of dysynchrony following TAVR [12]. However, eye-balling SF was not performed and a subtle SF may not have been captured with the longitudinal strain analysis, as explained above [12]. Another unresolved issue is whether SF itself contributes to the reshaping of the LV phenotype in typical LBBB. This intriguing question could be addressed in animal studies, simulation models and follow-up studies in patients with new onset LBBB.

SF and understanding variable responses to CRT

With the reappraisal of SF and recent studies on LBBB, new insights have emerged on how CRT improves LV function in LBBB [50,51]. Super responders with respect to reverse remodelling are a well-recognized population in CRT. Recent reports suggest that in these patients, LBBB itself causes the CMP as described above. Following CRT implant, not only is synchrony restored (with disappearance of SF), but also the septal wall thickness and contractility is markedly improved [46]. This is probably because the electrical activation of the septal wall is restored, instead of the abnormal right-to-left transseptal activation in LBBB accompanied with SF [26,52]. Moreover, the disappearance of SF probably indicates that normal septal activation is restored irrespective of “biventricular” or ‘LV pacing only”. The pathophysiological substrate of SF could explain why LV pacing only can restore SF-dysynchrony: the LV paced ventricle propagates the depolarization front from the left to the right side of the septum, making SF disappear and restoring septal function. This fits with previous work from Little et al., where LV pacing prevents the leftward motion of the septum in contrast to RV pacing [53]. Likewise, using MRI, Prinzen’s group illustrated similar effects of RV versus LV pacing on the septal work [52].

Thus, a major modus operandi in CRT is normalization of the septal wall activation, which results in disappearance of SF and restoring septal function and thickness, as long as the activation front is more or less restored from left to right in the septum [45,50]. As a consequence, there appears no absolute requirement for biventricular pacing to restore SF-dysynchrony and septal function. In fact, His-bundle pacing may even become the alternative for a LV lead in the future, as His-bundle pacing restores the QRS complex in many patients with BBB [54–56].

Finally, the concept of SF also explains why RV pacing could be deleterious in some: right-to-left septal activation can result in SF and septal hypocoaptactility [57]. Conversely, if the RV lead tip would approximate and quickly activate the LV subendocardial conduction system, normal septal activation will occur and SF and septal hypocoaptactility may not appear [52]. In this regard, a deep septal screw-in of the RV lead, a transeptal lead or His-bundle pacing results in a normal left-to-right septal activation and prevents SF and septal hypocoaptactility [58]. These considerations consequently explain why RV pacing is not per se deleterious, as long as the LV conduction system is quickly activated following the electrical impulse of the RV lead.

Based on the insights on LBBB/SF, we may now better understand why a spectrum from harm, no response to super response can occur following CRT implant, apart from many other variables that may affect CRT response. In Fig. 3, we propose 6 different hypothetical scenarios in patients with systolic heart failure, and how response (reverse remodelling) may vary following CRT implant, depending on the presence-absence of LBBB/SF and apart from many other variables affecting CRT-induced reverse remodelling. In Fig. 3A, severe LV dysfunction is primarily caused by LBBB itself and complete reverse remodelling ensues following CRT [super responder [46]]. In Fig. 3B, we hypothesize that the LV dysfunction caused by LBBB itself has evolved to an advanced stage and cannot fully reverse following CRT. In Fig. 3C, the LV dysfunction is caused by both a cardiomyopathic process and LBBB-induced LV remodelling. Here, we hypothesize that only the LBBB-induced dysfunction/remodelling can be reversed by CRT, but clear proof is lacking on this issue. Although it was shown that heart failure patients with LBBB but without SF (Fig. 3D) demonstrate much less reverse remodelling [14], these patients remain a clear CRT target according to the guidelines. Patients without LBBB (and thus no SF) (Fig. 3E) remain a difficult target population with low evidence of CRT benefit, but further research in this field is mandatory [59].

Is there any room left for SF as dysynchrony parameter in the field of CRT?

In the last decade, improvements in CRT have been realized based on the identification of clinical (gender, renal dysfunction), myocardial (scar), electrical issues (better identification of LBBB, device-related issues (programming, lead position), and innovations in CRT devices (multipolar electrodes, synchronizing algorithms) that are related to CRT response [60]. The recent studies of LBBB and SF have also shed important insights in LBBB electro-mechanics, LBBB-induced CMP and mechanisms of LV function recovery and reverse remodelling with CRT. Moreover, because a gold standard for detecting dysynchrony is lacking, SF may have a prominent role as dysynchrony parameter because it has been validated in outcome studies, it reflects an electrically-based mechanical dysynchrony pattern (thus amenable for CRT), and it was shown to be superior to the previous echo-dysynchrony methods in predicting CRT response [11,14,16]. In fact, most of the echo-dysynchrony methods such as TDI, M-mode, etc. were not validated with gold standard approaches for dysynchrony, yet they have been widely applied by investigators and clinicians [8]. Also, dysynchrony between two single myocardial segments sufficed to score dysynchrony as relevant, which is questionable as this represents only a minor fraction of the LV mass. On the contrary, in

Please cite this article as: S. Calle, C. Delens and V. Kamoen et al., Septal flash: At the heart of cardiac dysynchrony, Trends in Cardiovascular Medicine, https://doi.org/10.1016/j.tcm.2019.03.008
SF the entire septal wall is/becomes mostly hypokinetic, which is a major LV mass that can be targeted and recruited with CRT. Finally, as SF is a fast, robust and reproducible “dyssynchrony eye-catcher”, it might also be used as a parameter to optimize CRT programming in individual patients. Therefore, we believe that SF and AR merit consideration as “reference dyssynchrony” markers.

Although SF provides major advantages for assessing dyssynchrony, it is rare in clinical practice that a single parameter harbors all of the predictive features of a pathology with respect to prognosis or therapeutic response. Neither SF escapes from this dogma. Indeed, response rates in CRT are also determined by variables that may inhibit SF from disappearing following CRT such as lead position, improper CRT programming, and the extent of reverse remodelling may also be affected because of myocardial scar or evolving cardiac disease. Some of these parameters are included in recent scoring systems such as the CAVIAR and LANDS scores that better predict responses than the individual parameters [15,16]. Yet, in these scoring systems, SF and AR have a dominant role, which again underscores the clinical relevance of SF and AR [15,16]. In a large retrospective and observational study, adding AR and/or SF to most current ESC and AHA CRT recommendations improved the prediction of volumetric CRT response and survival rates in all guideline-recommended classes [61]. Moreover, 41% of patients who were not recommended for CRT implant showed improved response rates. This indicates that there is potential room for improving sensitivity and specificity of current CRT guideline criteria. On the other hand, it remains to be explored why and how CRT may provide benefit (reverse remodelling/clinical benefit) in patients with LBBB without SF or AR.

**SF: future perspectives**

First, a better understanding of the natural history and interaction between the onset of LBBB, SF and LV dysfunction is mandatory. Secondly, although SF appears to be a promising concept and may help in predicting CRT response in observational studies and retrospective studies, randomized prospective multicenter trials may be required. The ongoing EuroCRT observational international study will test the role of CMR and modern echocardiographic-updated parameters (including SF and AR) to predict the response to CRT among patients implanted according to the current guidelines [62].

Please cite this article as: S. Calle, C. Delens and V. Kamoen et al., Septal flash: At the heart of cardiac dyssynchrony. Trends in Cardiovascular Medicine, https://doi.org/10.1016/j.tcm.2019.03.008
Another merit of SF is that it attracted our attention to the pathophysiology of LBBB and its association with the LBBB-remodelled ventricle with decreased EF. As not all patients with SF develop significant LV dysfunction, risk factors (genetic, hemodynamic) that modulate LBBB-induced remodelling and CMP remain to be explored. Interestingly, a recent observation suggested increased afterload sensitivity (arterial hypertension) in patients with LBBB, as hypertension was shown to play a role in the pathophysiological reverse remodelling of LBBB [63].

Finally, the underlying cellular and molecular events governing the LBBB-reshaped ventricle are of interest [40]. Unravelling these events may lead to the identification of a typical molecular signature in the septum, and comparisons of the molecular biology to other cardiomyopathies or hypertensive myocardium may be informative. These findings could be a benchmark for molecular imaging and pharmacological innovations to target specific cardiomyopathic pathways.

Acknowledgements

All authors declare that they have no conflict of interest. All authors declare that they do not receive grants for research purposes.

References


