Optimal Use of Echocardiography in Management of Thrombosis After Anterior Myocardial Infarction

Andrea Barbieri[1], francesca mantovani[2], Francesca Bursi[3], Andrea Faggiano[4], Giuseppe Boriani[1], and Pompilio Faggiano[5]

[1]Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena
[2]Azienda Unità Sanitaria Locale - IRCCS Tecnologie Avanzate e Modelli Assistenziali in Oncologia di Reggio Emilia
[3]Azienda Ospedaliera San Paolo
[4]Università degli Studi di Milano
[5]Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

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Abstract

Despite advancement in therapy and management, left ventricular thrombus (LVT) after anterior myocardial infarction (MI) is sporadically encountered and remains associated with a very high risk of major cardiovascular events and mortality. Cardiac magnetic resonance (CMR) is considered the gold standard technique for LVT detection, but it is a time consuming and expensive test not available in all centers, especially when repeated exams are necessary. Transthoracic echocardiography represents a useful tool to screen for LVT and to identify predictors of high risk of developing LVT. The advances in ultrasound technology and the use of contrast agents may potentially help clinicians to identify LVT and the use of sequential echocardiography for each patient with acute MI complicated by LVT may provide an opportunity to quantify regression and its correlation with outcomes to tailor the management of these patients. Hence, this narrative review focuses on the added value of echocardiographic-guided LVT management in patients with recent anterior MI to reduce mortality and morbidity excess related to LVT based on current evidence.

Diagnosis

A detailed assessment of LVT is crucial for patient management and prognosis. Cardiac magnetic resonance (CMR) is now considered the diagnostic standard for detection of LVT with cine-CMR and contrast-enhanced CMR (CE-CMR) being the most useful modalities (Fig.1). This is particularly true in patients with mural or small LVT.[12] The only study that included surgical or pathological evidence of LVT for confirmation of LVT showed that CE-CMR has a diagnostic sensitivity of 88% and specificity of 99%.[13] No other study has subsequently shown that an alternative modality is superior to CE-CMR imaging in LVT detection.[14]

Cardiac magnetic resonance imaging has not only the strength to provide better spatial resolution for morphological definition[15] but can characterize and differentiate the avascular LVT from neighboring structures after contrast administration. Moreover, CE-CMR can distinguish between acute versus older thrombus (Fig.1). Newer CMR sequences (such as T2* to identify ferrous products of hemoglobin breakdown and the use of long inversion time imaging to selectively null the normal myocardium) may provide further diagnostic advantages above and beyond CE-CMR imaging.[16, 17]

Contrast-enhanced CMR proved that an imaging delay after acute MI of more than 5 days was associated with significantly higher LVT detection rates compared to imaging performed within 5 days. Of note,

CE-CMR performed between 9–14 days post-MI provided the highest detection rate.[18, 19]

Despite its diagnostic superiority, CMR remains a time consuming and expensive test, not available in all centers. Indeed, it is impractical to perform and repeat CMR in all patients with high-risk MI. A more practical approach may be to perform a transthoracic echocardiography (TTE) as the first-line imaging modality to screen for LVT in all patients with recent MI. Accordingly, current European Society of Cardiology guidelines recommend routine TTE during hospital stay in all patients to exclude LVT after MI (Class I, Level B).[20]Furthermore, considering that LVT could develop at various times after MI, performing repeated TTE rather than a single CE-CMR could have an even greater clinical impact in patients with satisfactory ultrasound quality.

The diagnosis of LVT by TTE should be defined as a mass in the LV cavity located adjacent to an area of LV wall dyssynergia and seen from at least two views (usually apical and short axis, Fig.2). Care must be taken to exclude the most common causes for an erroneous diagnosis of a thrombus (false tendons, trabeculae, technical artifacts and tangentially-cut LV wall).[1, 12] Usually, LVT have a homogeneous texture with a softer echo density than myocardium, which suggests that the thrombus may be relatively recent and still "in a growing phase", whereas an older thrombus tends to have a smoother surface and is typically more static.[21]

On the basis of available data it is possible to extrapolate that, in comparison with CE-CMR, non-contrast TTE has a sensitivity of 24%-33%, a specificity of 94%-95%, an accuracy of 82%, a positive predictive value of 57% and a negative predictive value of 85%.[14] A low sensitivity may be of concern because TTE is the examination performed regularly in daily practice to search for LVT. However, it is difficult to generalize these data to the current "real life" since previous studies evaluating TTE used multiple gold standards, or none at all, and were conditioned by subjective image quality and the use of the off-axis projections.[14] Indeed, TTE is more operator-dependent than CE-CMR. Varying gain setting and depth of field, as well as using transducers with different frequencies in multiple positions and orientations, are helpful approaches to minimize the false-positive studies. This important notion is highlighted by the finding that TTE performance varies highly according to the exam indication: if LVT search is prespecified, sensitivity is multiplied by 2 (60% vs. 26%) and positive predictive value by 3 (75% vs. 21%) as compared with unfocused routine TTE.[22] When the search for LVT is prespecified in high-risk patients with recent anterior MI and low ejection fraction, the accuracy of TTE as compared with DE-CMR is even better (sensitivity and specificity 94.7% and 98.5%, respectively).[19] Thus, we believe that the attempt to uncritically combine results from the literature to provide a summary estimate of the diagnostic accuracy of TTE might have led to inaccurate or misleading results, at least when considering Echo labs with high standards of quality in TTE. Indeed, considering the importance of the echogenicity, TTE ideally should be scored for diagnostic quality using previously validated quantitative tools.[12]

In short, we must emphasize that TTE accuracy can be excellent if performed specifically for LVT search with a standardized protocol and that non-visualized LVT are usually mural and small (Table).

Role of new echocardiographic technologies

Over the past decade, we have witnessed a development in the armamentarium of echocardiographic technologies capable of providing even more detailed information about LVT. Many of these features allow an integrative approach, as they combine the unique strengths of the single technologic component to achieve unprecedented improvement in our ability to diagnose LVT by TTE. Real-time three-dimensional echocardiography (RT3DE) provides an unlimited ("panoramic") number of cutting planes in all directions through a single full volume data set (Fig.3). Therefore, cropping and rotating the volumetric data set allow to obtain the perspective that best visualizes a LVT and its attachment to the LV wall. The chance to re-align the tomographic planes obtained from a RT3DE dataset reduces the risk of missing small apical thrombi due to the foreshortening of apical views with two-dimensional TTE.[23, 24] However, RT3DE does not allow to differentiate between LVT and myocardium nor to assess the changes in thrombi structure, as it is known that with RT3DE the different shades of blue/brown color give a visual perception of the depth of different structures rather than their texture.

The advent of ultrasound contrast agents, providing the opacification within the cardiac chambers to demonstrate the avascular "filling defect" appearance of an intracardiac LVT, has been critical.[25] Indeed, it is now proven that the use of ultrasound contrast agents greatly improves the diagnostic accuracy of TTE from 82% to 92% when compared to CE-CMR.[14]

Screening algorithm

In patients with uncomplicated anterior MI it is advised to carry out a LVT screening before discharge. Recently, a TTE-based wall motion screening algorithm for LVT has been proposed, able to assesses the extent of apical wall-motion abnormalities using the 17-segment model. Apical LV wall motion score is then calculated on non-contrast echo by summing segmental scores within the apical LV and true apex (total of 5 segments). An apical wall motion score [?]5 can identify patients with a high likelihood of LVT, thus to be referred eventually for CE-CMR with a high diagnostic yield, regardless of LV global contractile function.[16] Therefore, given cost containment, a pre-discharge TTE-based screening approach should be implemented: contrast-enhanced TTE could be performed instead of CE-CMR in all patients with high-risk apical wall motion score, especially in patients with poor ultrasound windows, and a CE-CMR could be reserved only when contrast-enhanced echo is non-conclusive. However, considering that the hospital stay of patients with uncomplicated MI has declined substantially in recent years[26] and therefore is shorter than the time needed for a LVT to be detected[26], it may be reasonable to repeat a TTE during the second week in patients with high-risk apical wall motion abnormality without LVT on initial imaging.

The alternative approach is to perform CE-CMR to all patients with high-risk apical wall motion score at non-contrast TTE. Of note, no specific screening pathway after anterior MI has been prospectively validated, therefore further validation before widespread application is required. A recent single-center retrospective case-match study showed that, despite contemporary antithrombotic treatment, a LVT detected by CE-CMR, but not by contrast TTE, is associated with a similar 4-fold long-term higher risk of embolism compared with matched non-LVT patients.[27] However, this study evaluated a heterogeneous cohort where only one-third of patients had a previous MI with a severely reduced ejection fraction. Because of the retrospective nature of the study, referral bias was inevitable and it was not feasible to obtain reliable measures of the efficacy of anticoagulation, such as the time in therapeutic range, in all LVT patients. Therefore, to address all these limitations, more studies are needed specifically comparing screening strategies based on contrast TTE or CE-CMR for detection of LVT in patients with recent anterior MI.

Risk stratification and prevention of systemic thromboembolism

Even in the primary angioplasty era, LVT formation after MI indicated a fourfold increased embolic risk and twofold long-term mortality rate.[28] The risk of embolic events is the highest during the first or second week after MI with a decline over the subsequent 3 months.[29-31] Thrombi prone to embolization are those that protrude in the LV cavity (exposed to the blood flow on several sides) and have a free mobility (which indicates thrombus friability), unlike the mural thrombi that appear flat and parallel to the endocardial surface (Fig.2).[32, 33]

Other echocardiographic LVT characteristics, such as thrombus size, central echolucency or hyperkinesia of the myocardial segments adjacent to the thrombus, were found to be associated with an increased risk of embolism in some studies, but were not confirmed by others.[1] However, it is critically important to appreciate that a spontaneous time-course variation in the LVT morphologic aspects is common in the first several months after MI (Fig.3). Importantly, up to 40% of embolism episodes occur in patients whose thrombi are neither protuberant nor mobile.[34]Therefore, when LVT is detected, anticoagulation is essential to prevent systemic thromboembolism regardless of the echocardiographic phenotype.

Current guidelines recommend vitamin K antagonists as the first-choice therapy in this patient population.[20, 35, 36]Thrombus resolution with warfarin occurs frequently (80-85% at 6 months) after an anterior MI. It could be argued that LVT regression may be at least partially the consequence of thrombus embolization. However, although asymptomatic embolization cannot be excluded, LVT regression seems not associated with increased embolic risk.[37]

The thromboembolic risk appears to be lower in the current reperfusion era, with a cumulative incidence of 5.5%.[6] This is due, at least in part, to the higher time in therapeutic range usually achieved during warfarin treatment. Indeed, the rate of systemic embolism is quite low (3%) in patients with a time in therapeutic range [?]50%.[38]

Of note, no data are currently available from clinical trials evaluating the safety and efficacy of anticoagulation in the treatment of LVT after MI. This gap in knowledge is important considering that the antithrombotic options for LVT have become more complicated for a series of reasons, including patient characteristics, with progressively older subjects, affected by multiple comorbidities, the need for a combination of chronic anticoagulation and various antiplatelet therapy schemes, and the emergence of direct oral anticoagulants (DOACs), widely used in the setting of thromboembolic prophylaxis for atrial fibrillation or pulmonary embolism. Therefore, clinicians must rely on available data from trials to guide the treatment of these different thromboembolic conditions, which substantially showed that the combination of oral anticoagulants with two antiplatelets (triple therapy) increases the bleeding risk compared with less potent antithrombotic regimens after MI. On the other hand, observational data suggest that triple therapy regimens may not prevent LVT formation.[21, 39]

The efficacy of DOACs in the treatment of LVT seems comparable to the efficacy of warfarin, but current data are limited to small case series and meta-analysis of case reports[40-42]. Nevertheless, the intrinsic differences in thrombogenesis between LVT and atrial fibrillation-related thrombi, either in the left atrium and its appendage, can make anticoagulants non-interchangeable and request a better assessment of the off-label use of DOACs in terms of benefits and risks. Indeed, the largest multicenter, retrospective study for LVT diagnosed by TTE argues against the assumption of equivalence between DOACs and warfarin.[43] Trials comparing DOACs and warfarin in the treatment of LVT are ongoing in China, Malaysia and Israel (ClinicalTrials.gov number NCT03764241, NCT02982590 and NCT03232398, respectively).

Echocardiography and clinical management

In patients with recent anterior MI and high-risk non-contrast apical wall motion score ([?]5), pre-discharge image enhancement with ultrasound contrast agents is recommended in the absence of contraindications. In those without LVT, one approach may involve a repeated TTE after [?] 2 weeks (Fig.4). If LVT is not detected on repeated TTE, anticoagulants are not indicated.[44] Conversely, in the case of detection of LVT, oral anticoagulants should be immediately started with a parenteral anticoagulant bridging. A combination of warfarin with single P2Y12 inhibitor (double therapy) may be preferred over triple therapy, in light of accumulating evidence suggesting the reduced bleeding risk of this approach from studies on patients with atrial fibrillation associated with acute coronary syndrome.[39] Hence, when used in combination with an oral anticoagulant, clopidogrel should be preferred above aspirin and more potent P2Y12 inhibitors. In patients at high risk of recurrent MI or stent thrombosis, a short course (e.g., 1 month) of triple therapy might be considered when balanced against the bleeding risk.

In patients with difficulty to maintain the therapeutic anticoagulation range with warfarin a full-dose DOAC may be preferred.[21]

The optimal duration of oral anticoagulation in patients with LVT after MI has never been tested in the era of dual antiplatelet therapy. According to current guidelines, anticoagulants should be added to antiplatelet therapy for a variable time of 3-6 months since the duration must be individualized according to bleeding risk.[20, 35, 36] At the end of this period, a repeated TTE with ultrasound contrast agents should be performed. If the LVT has resolved, anticoagulants can be dismissed while continuing DAPT. Nevertheless, a prudent approach with an additional TTE with ultrasound contrast after a further 3 months is suggested. In the case of LVT recurrence at any time, long-term anticoagulation must be maintained unless other contraindications. In patients without LVT resolution or persistent apical spontaneous echo-contrast, the optimal therapeutic management is unclear, and decision regarding continuation of oral anticoagulation should be made on a case-by-case basis (Fig.3).

Recently, a real-world post hoc analysis from a single-center study with independently verified LVT (mainly

diagnosed by TTE) indicated that thrombus regression, which occurred in 62.3% of cases, represents a strong independent marker of lower morbidity and mortality. Conversely, patients with persistent LVT were at high risk of clinical complications even when combining with antiplatelet agents.[11] The observation that in this cohort as many as 1/3 of patients did not achieve total LVT regression and that even 14.5% had recurrent or increased size of LVT emphasize the need for more efficient therapeutic strategies to improve and accelerate LVT regression. Yet, any intensification of the antithrombotic treatment may be compromised by more frequent and more severe bleeding complications. Therefore, an individualized risk stratification based on patient characteristics and LVT evolution under TTE guidance could be the ideal decision-making approach. However, only a prospective, randomized controlled trial may detect and quantify the advantages of anticoagulation intensification versus long-term maintenance of standard anticoagulation in these cases.

Conclusive remarks

Current echocardiographic-guided screening and management strategies for LVT in patients with recent anterior MI warrant to be re-evaluated in light of the advances in technology which greatly improve the diagnostic accuracy of this approach as compared to CE-CMR. However, this pathway relied on resolution on TTE as evidence of treatment effect requires prospective validation since many questions, such as the prognostic significance of LVT detected by CE-CMR but not by contrast TTE, are still unanswered. In some cases, a LVT can be a marker of an increased thrombotic risk that persists at the long term, after the initial period of anticoagulation and even despite thrombus resolution by TTE. This knowledge could guide the selection of the optimal imaging modality for the screening of patients with recent anterior MI at high risk for LVT. Hopefully, this work might strengthen the role of echocardiography in the management of these patients.

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Figures' legend

Figure 1. Typical example of left ventricular thrombosis assessment by dedicated cardiac magnetic resonance after anterior myocardial infarction.

Patient example. Panel A: Patients with transmural anterior infarction with older mural thrombus (low signal intensity in T1 in cine cardiac). Panel B, C: acute protruding thrombus in the left ventricular apex (yellow arrow) showing high signal intensity on T1. Panel D: phase sensitive contrast-enhanced magnetic resonance images. Panel E: contrast-enhanced magnetic resonance images: note that thrombus appears black on long inversion time (T1).

Figure 2. Different morphological left ventricular thrombi aspects detected by transthoracic echocardiography.

Panel A: 4-chamber apical view showing a left ventricular mural thrombus visible as a minus image (asterisk) because of contrast agent. Panel B: a protruding left ventricular thrombus visualized before (arrow) and after contrast injection (asterisk). Panel C: a large protruding and free mobile left ventricular thrombus before (arrow) and after contrast injection (asterisk).

Figure 3. Left ventricular apical thrombus detected by echocardiography 15 days after acute anterior myocardial infarction.

Panel A: 4-chamber and 2-chamber apical views showing a large protruding LV apical thrombus (asterisk) in an akinetic LV apex. Note soft density and irregular shape typical of recent thrombus Panel B: after contrast injection, the thrombus is visible as a minus image (asterisk). Panel C: full volume RT3D apical view oriented from the LV apex, shows the spatial definition of LV thrombus. Panel D: multislice multiplane

view of LV apex with thrombus attached to the apical septal and apical inferior segments. Panel E: follow-up echocardiogram after 3 months of anticoagulant therapy showing almost complete resolution of the apical thrombus but residual shallow mural thrombus with smooth and hyperechogenic surface visible in the apical 2 chamber view (arrow) in the akinetic LV apex. Data on the embolic avoidance and subsequent antithrombotic management in patients who did not achieve total LVT regression are limited or lacking.

Figure 4. Transthoracic echocardiography-based flow chart for guiding LVT management after anterior myocardial infarction. Note that for many decision-making there is no scientific evidence. Therefore, the proposed algorithm is inevitably, for the most part, based on the opinion and clinical practice of the authors.

WMSI: wall motion score index; LVT: left ventricular thrombus; AC: anticoagulation therapy; TTE: transthoracic echocardiography; LV: left ventricle; SEC: spontaneous echo-contrast.

Table and table's legend

Table . Imaging modalities used to diagnose left ventricular thrombus after myocardial infarction.

	Sens	**Spec**	**PPV**	**NPV**	**Accuracy**	**Gold standard confirmation**	**Prior MI**	**Referenc**
CE-CMR	88%	99%	NA	NA	NA	Surgical/Pathological	100%	#13
TTE*	60%	88%	75%	78%	77%	CE-CMR	100%	#22
TTE**	94.7%	98.3%	NA	NA	NA	CE-CMR	100%	#19
Contrast TTE	61%	99%	95%	91%	92%	CE-CMR	83%	#12

* Left ventricular thrombosis search prespecified.

**Left ventricular thrombosis search prespecified in recent anterior myocardial infarction and low ejection fraction.

CE-CMR: contrast-enhanced cardiac magnetic resonance

TTE: transthoracic echocardiography

MI: myocardial infarction

NA: not available

PPV: positive predictive value

NPV: negative predictive value

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