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Reconstructive

Utility of Viscoelastic Tests to Predict Flap Thrombosis: A Systematic Review

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Background: Flap thrombosis is a rare but devastating complication in microsurgery. Preoperative identification of patients at increased risk for microvascular thrombosis remains challenging. Viscoelastic testing (VET) provides a comprehensive evaluation of the clotting process and can effectively identify hypercoagulability. However, the utility of VET in microvascular reconstruction remains unclear.
Methods: A systematic review of the association between VET and pedicle thrombosis and free flap loss was performed in accordance with Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. Identified studies were reviewed independently by two authors for pertinent data.
Results: Six studies met inclusion criteria. Heterogenous study design and outcome reporting complicated direct comparisons and precluded a formal meta-analysis. Four studies found a statistically significant relationship between VET results and flap thrombosis or flap loss. The maximum clot strength and the fibrinogen-to-platelet ratio (FPR) were key viscoelastic parameters in these studies, both representing a measure of maximal clot strength. Specifically, an elevated FPR (>42%) generated a sensitivity and specificity for flap loss ranging from 57% to 75% and 60% to 82%, respectively. Notably, the negative predictive value for flap failure with a normal preoperative FPR was greater than 90% in all studies reporting a correlation. The remaining two studies reported no predictive value for VET with respect to flap failure or pedicle thrombosis.
Conclusion: The results of this review suggest that VET, particularly parameters relating to clot strength, may help clinicians identify patients at risk for flap thrombosis. However, uncontrolled and heterogenous reporting limit definitive conclusions, and high-quality diagnostic studies are needed to better determine the clinical utility of viscoelastic testing for free flap patients. *(Plast Reconstr Surg Glob Open 2021;9:e3769; doi: 10.1097/GOX.0000000000003769; Published online 12 August 2021.)*

INTRODUCTION

Since the first described free flap in 1973, microvascular free tissue transfer has rapidly become an invaluable tool in the reconstructive armamentarium.[1,2] As technique and technology have improved, the success rate of free flaps has risen to over 98% in both university and community hospital settings.[3] Although rare, complete flap loss can be devastating for the surgeon and patient alike. Flap necrosis most commonly occurs as a result of microvascular thrombosis.[4] The ability to identify hypercoagulable patients who are predisposed to microvascular thrombosis preoperatively would enable targeted preventative measures and improve outcomes.

It is estimated that over 10% of the general population carry an underlying hereditary thrombophilia, many of whom remain asymptomatic and go undiagnosed for life. Even more patients present with acquired hypercoagulability stemming from a broad range of conditions including malignancy, smoking, trauma, and hormonal imbalances.[5] In light of the high prevalence of undiagnosed hypercoagulable states, it remains difficult to predict which patients will experience thrombotic complications and may benefit from anticoagulation.[6,7]

Conventional preoperative coagulation tests such as prothrombin time, activated partial thromboplastin time, and platelet count provide only a quantitative snapshot

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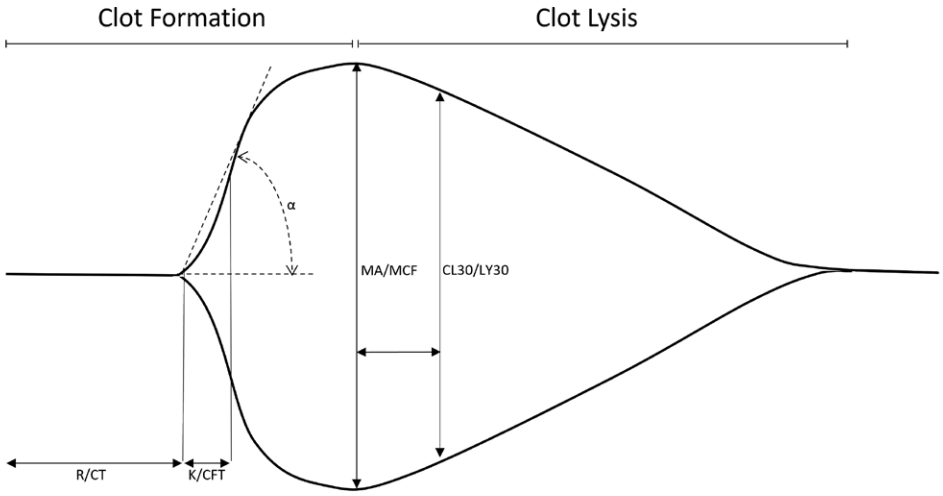
of isolated components in a vastly complex clotting cascade. They do not provide information on the functional manifestations of these isolated elements on the clotting cascade as a whole.[8] Furthermore, the turnaround time of these standard tests is around 45 minutes resulting in suboptimal efficiency, especially in the acute setting.[9] Due to these issues, it has been difficult to use these tests to predict hypercoagulability, and they are not currently recommended as a screening tool.[6]

More recently, viscoelastic testing (VET) has emerged as a promising alterative that measures qualitative aspects of the clotting process from clot formation, propagation, maximum clot strength, and clot dissolution. Results regarding clot formation can be generated in as little as 10 minutes and may be more cost effective than conventional laboratory tests.[10,11] VET was adopted for clinical use in liver transplantation in the 1980s but did not receive significant interest until the beginning of 21st century when clinical utility was demonstrated in guiding trauma transfusions.[12,13]

Testing is performed by placing whole blood samples in a chamber with a detection pin. The sample is oscillated and the resulting deflection of the center pin is measured as the increasing viscoelastic properties of forming clot deflects the pin.[14] Two widely used VET systems are Thromboelastography (TEG) and rotational thromboelastometry (ROTEM).[15] They measure the same fundamental viscoelastic changes throughout the clot life cycle, but report different parameters and reference values (Fig. 1).[16] A representative tracing is produced depicting the evolving shear elasticity of the clot with several key timepoints. The time from initiation of the test until the earliest detectable deviation of the pin (2 mm) is referred to as the clotting or reaction time and marks the first formation of clot elements. Clot kinetics describes the time it takes for the clot to increase in strength sufficiently to deviate the pin 20 mm. The angle at which the tracing separates, termed alpha angle, depicts the rapidity of fibrin activation and clot buildup. The maximal clot strength is measured, and the degree of clot lysis is marked 30 minutes after maximal clot strength was achieved.

The addition of various reagents can isolate the functionality of different segments of the clotting pathway. For instance, the functional fibrinogen-to-platelet ratio (FPR) can be measured to evaluate the contribution of fibrinogen to clot strength through the addition of a platelet inhibitor such as abciximab or cytochalasin D.

The utility of VET to identify hypocoagulability and guide blood product transfusions in trauma, hepatology, transplantation, and cardiac surgery is well defined, but its ability to provide meaningful results in microsurgery has not been clearly elucidated.[17–19] The objective of this systematic review is to evaluate the efficacy of VET to predict microvascular thrombotic complications and flap failure.



TEG®	ROTEM®	Definition	Significance
Reaction time (R)	Clotting time (CT)	Time from initiation until first detectable clot formation (2mm of amplitude)	Activation phase: time needed to activate intrinsic pathway. Depends on plasma concentration of clotting factors
K time	Clot formation time (CFT)	Time for the amplitude to increase from 2mm to 20mm	Amplification phase: speed of initial fibrin deposition and crosslinking
α angle	α angle	Slope of the line between R/CT and K/CFT	Propagation phase: characterizes the maximal speed of thrombin generation and is depending on fibrinogen concentration
Maximum amplitude (MA)	Maximum clot firmness (MCF)	Greatest vertical width of the tracing reflecting the maximum clot strength	Termination phase: maximal strength of the clot. Depends on the number and function of platelets and fibrinogen
CL30	LY30	Percent reduction in amplitude 30 min after maximal clot strength	Fibrinolysis phase: clot stability and fibrinolysis

Fig. 1. Diagram of a typical viscoelastic tracing demonstrating the dynamic changes throughout the clot life cycle.

METHODS

A systematic review on the association between VET and flap loss or pedicle thrombosis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Fig. 2).[20] The PubMed, Embase, Cochrane Library, Web of Science, and Scopus databases were searched on May 20, 2020, using keywords connected with Boolean operators. The complete search strategy is described in the **Appendix, Supplemental Digital Content 1**, which displays the search strategy. **http://links.lww.com/PRSGO/B763**. Manual search of articles was also conducted to identify articles. The resulting articles were evaluated through title and abstract screening, and full-text review of relevant articles was conducted. Information on patient characteristics, timing and features of viscoelastic tests, and outcomes were collected using a standardized data collection form. We excluded review articles, letters to the editor, abstracts, and case reports.

RESULTS

A total of 142 articles were retrieved from PubMed, Embase, Cochrane, Web of Science, Scopus databases, and manual search. Through title and abstract screening, 11 articles were selected for full-text review. During full-text screening, four literature reviews and one case report were excluded.[21–25] The remaining six studies matched the inclusion and exclusion criteria and were included for review (Table 1). Significant heterogeneity was noted in study design, interventions, and outcome data reporting, precluding a meta-analysis. Of note, many studies reported only partial VET results, and many used different reagents and activating factors to perform subtests, further complicating data analysis and interpretation.[26]

Parker et al[27] retrospectively analyzed 29 patients that received 35 head and neck free flaps to determine if preoperative FPR values could predict thrombotic flap complications. The authors did not elaborate why FPR was selected for testing as opposed to the standard TEG

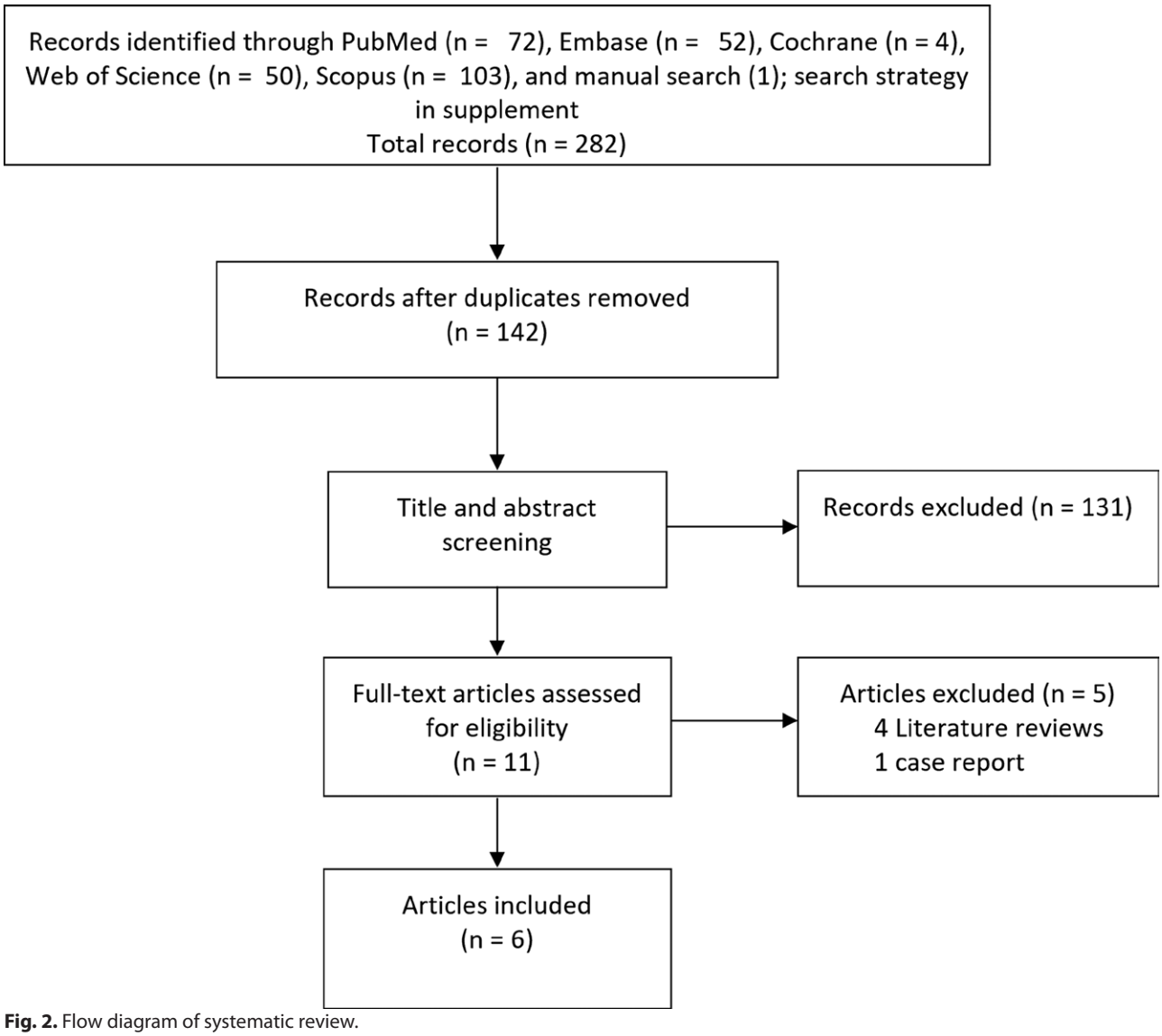


Fig. 2. Flow diagram of systematic review.

Table 1. Summary of Included Studies

Study Design	Population Characteristics	Viscoelastic Testing	AC Protocol	Flap Loss	Pedicle Thrombosis	Conclusions	Notes
Parker et al[27] Retrospective cohort	Patients: 29 free flaps: 35 Indication: H&N cancer	TEG: FPR	Not standardized	4 (11.4%)	9 (26%) Arterial (2), Vein (7)	FPR ≥ 42% was associated with increased risk of flap thrombosis ($P = 0.003$)	Sensitivity 89%, specificity 75%
Kolbenschlag et al[28] Retrospective cohort	Patients: 181 Free flaps: 181 Indication: varied	ROTEM: MCF, FPR	Not standardized. Heparin 15,000U/d or LMWH BID postoperatively	14 (7.7%)	28 (15%) Arterial (6), Vein (15), both (7)	Elevated MCF and FPR >43 was associated with flap thrombosis (P=0.036 and 0.003, respectively)	Odds ratio for flap failure: Elevated MCF, OR = 3.75 FPR >43, OR = 7.9
Vanags et al[29] Prospective cohort	Patients: 103 Indication: trauma	ROTEM: CT, CFT, MCF, FPR	Enoxaparin 40 mg daily		16 (15.5%)	FPR ≥ 42 was associated with flap thrombosis ($P = 0.003$) in the delayed reconstruction cohort only	The acute reconstruction cohort was underpowered
Zavlin et al[30] Retrospective cohort	Patients: 171 Indication: breast reconstruction	TEG	Dosing based on TEG-G. Intraoperative: IV heparin Postoperative: LMWH	2 (1.2%)	5 (2.9%) Arterial (1), Vein (4)	TEG-G > 10,900 was associated with flap thrombosis ($P = 0.049$)	Elevated preoperative TEGs were prophylactically treated with higher dose heparin
Ekin et al[31] Retrospective Case series	Patients: 77 Free flaps: 77 Indication: varied	TEG	Not standardized	3 (3.9%)	5 (6.5%)	TEG was not associated with flap thrombosis or flap complications	No hypercoagulable patients were included in the study
Wikner et al[30] Prospective cohort	Patients: 35 Free flaps: 35 Indication: H&N cancer	ROTEM: INTEM CT, EXTEM CT	Intraoperative IV heparin, adjustment based on pTT	3 (8.6%)	5 (14.3%)	ROTEM values did not correlate with flap thrombosis or loss	ROTEM exhibited a dose response to IV heparin

AC, anticoagulation; AUC, area under the curve; BID, twice a day; CT, clotting time; gtt, drops; EXTEM, extrinsic pathway ROTEM parameter; HN, head & neck; INTEM, intrinsic pathway ROTEM parameter; IV, intravenous; POD, postoperative day; pTT, partial thromboplastin time; RTE, rotational thromboelastometry; SIEV, superficial inferior epigastric vein; TEG-G, thromboelastography log-derivation of maximum amplitude parameter; TEG-K, thromboelastography kinetics parameter; TEG-R, thromboelastography reaction parameter; TEG-SP, thromboelastography split point parameter.

reference values. Anticoagulation protocols were not detailed, but IV heparin was given to those with intraoperative thrombosis. In total, nine patients (31%) experienced a thrombosis within the pedicle or recipient vessels. Four of these were noted intraoperatively and five thromboses were detected postoperatively. Baseline FPR values were significantly higher in the patients with thrombotic events (47±7% versus 37±5%). A threshold of FPR ≥ 42% was found to have a sensitivity of 89% and specificity of 75% for predicting thrombotic events. There were four patients (13.8%) with flap loss; however, no statistical significance with respect to FPR values was noted.

Similarly, Kolbenschlag et al[28] evaluated the predictive value of FPR and ROTEM by retrospectively analyzing flap outcomes in 181 free flap patients. Patients were deemed hypercoagulable based on elevated preoperative ROTEM or FPR values. Postoperative anticoagulation was given based on surgeon's judgment and consisted of either continuous unfractionated heparin (UFH) infusion or subcutaneous low molecular weight heparin (LMWH). A total of 28 (15.5%) patients experienced flap thrombosis, and 14 (7.7%) patients experienced flap loss. Although continuous UFH was administered to a majority (although unspecified number) of the patients with pathological ROTEM findings, they reported that both an abnormal preoperative ROTEM or FPR greater than 43 predicted flap loss (OR: 3.75, $P = 0.036$ and OR: 7.9, $P = 0.003$, respectively).

In the most recently published study, Vanags et al[29] also evaluated the predictive value of FPR derived from ROTEM for free flap thrombosis in the trauma population. One hundred three patients underwent free flap reconstruction for traumatic defects, most frequently of an extremity (94%). Preoperative hypercoagulability, defined as FPR of 42 or greater, and rates of flap thrombosis were compared between patients undergoing flap reconstruction acutely (within 30 d of trauma, n = 36) or in a delayed fashion (n = 67). Standard postoperative thrombosis prophylaxis with enoxaparin 40 mg daily was given to all patients irrespective of individual risk factors. A preoperative FPR of 42 or greater was correlated with a higher free flap thrombosis rate (r = 0.362, $P = 0.003$) with an odds ratio of 8.83 (confidence interval 1.74–44.76, $P = 0.009$) in the delayed surgery cohort. Interestingly, FPR of 42 or greater was not a statistically significant risk factor for flap thrombosis in the acute surgery cohort, which exhibited higher rates of baseline hypercoagulability as compared to the delayed surgery group (44% versus 23%, respectively) and was not sufficiently powered to detect a difference in this subgroup.

Zavlin et al[30] retrospectively reviewed their institution's experience using a TEG-guided anticoagulation protocol to evaluate the relationship between perioperative TEG and microvascular complications in breast reconstruction. Patients were categorized as hypercoagulable if the G value (log-derivative of maximal clot strength) was greater than 10,000 dyn/cm^2. Anticoagulation protocols were altered based on perioperative G values. An elevated preoperative G was treated with increasing doses of IV intraoperative heparin and postoperative G values guided subcutaneous LMWH dosing. Elevated preoperative G values were found to return to baseline after the administration of high dose

IV heparin intraoperatively. There were five patients with pedicle thrombotic events, three of which were salvaged, resulting in a flap failure rate of 1.2%. Those with thrombotic events did not have higher preoperative TEG-G than controls (8464 ± 1482 versus 9484 ± 1862; $P = 0.233$), which supports the author's hypothesis that TEG-guided anticoagulation protocols may mitigate the risk of flap thrombosis. Postoperative G values increased in all patients but were found to be more significantly elevated in patients that experienced thrombotic complications. Conversely, conventional coagulation testing showed only minor changes throughout the perioperative course.

Ekin et al[31] retrospectively assessed the relationship between TEG results and complications in a diverse microvascular free flap cohort of 77 patients. Preoperative and postoperative TEG and conventional coagulation results were analyzed; however, the timing of postoperative draws varied. Furthermore, anticoagulation protocols were not standardized or based on laboratory results. Five patients experienced a thrombotic flap complication. All had normal preoperative TEGs and four had normal preoperative conventional coagulation tests. The authors were unable to define a clear relationship and noted that the timing of perioperative hypercoagulability testing and anticoagulation protocols should be standardized in future studies.

Through a prospective cohort study, Wikner et al[32] sought to determine if conventional coagulation testing or ROTEM could predict bleeding, flap thrombosis, or flap loss. They tested 35 patients with malignant head and neck tumors preoperatively, at the time of anastomosis, and 24 hours postoperation. Approximately 90 minutes before the anastomosis, all patients received IV heparin (200 mg/kg/d) irrespective of preoperative results. Subsequently, IV heparin was dosed based on pTT (goal 40–60 s). Five patients experienced flap thrombosis. Viscoelastic properties exhibited a dose response to IV heparin; however, neither ROTEM nor conventional coagulation testing were capable to predicting adverse events.

DISCUSSION

With the increasing incidence of free flap reconstruction, it is critical to address the issue of flap loss in microsurgery. Although many factors including surgeon experience influence flap thrombosis, identification of patients predisposed to flap thrombosis may enable more targeted anticoagulation to reduce thrombotic events and spare lower risk patients from bleeding complications. As an alternative to standard laboratory tests, viscoelastic tests have been used to predict flap thrombosis and flap loss due to their characterization of the global clotting process, cost-effectiveness, and speed. This systematic review attempts to compile the evidence on the use of viscoelastic tests in predicting flap thrombosis and flap loss.

Of the six relevant studies analyzed, four studies demonstrated a significant relationship between VET parameters and thrombotic complications. Three identified that an elevated FPR was associated with flap loss or thrombosis.[26–28] The fourth study used a TEG-guided anticoagulation protocol and found that TEG values responded appropriately to anticoagulation in patients with elevated preoperative values. Moreover, elevated postoperative G values, a measure of maximal clot strength, were significantly associated with an increased risk of thrombotic complications.[30]

The remaining two studies in this review did not find a statistically significant relationship between VET parameters and flap thrombosis, but these findings have significant limitations. One study included no hypercoagulable patients, suggesting that the analysis was insufficiently powered.[31] Furthermore, in the postoperative period, there was no standardized protocol for sample collection, and 73 of 77 patients received unspecified anticoagulant therapy. The second study only utilized one viscoelastic parameter (clotting time) and reported no information on clot strength.[32] Several studies found no correlation with clotting time, but did identify relationships with parameters measuring the clot strength. Thus, studies not evaluating these variables may fail to identify meaningful associations.

The findings from the six published studies suggest that FPR and TEG-G, both of which are measures of maximal clot strength, may provide clinically significant predictive value for flap loss and thrombosis due to hypercoagulability. It is unclear why clot strength may be predictive of microvascular thrombosis as opposed to other viscoelastic parameters. In particular, the fibrinogen contribution to clot strength (FPR) was predictive of flap loss and/or thrombosis in three studies, although none of the studies elaborated on why FPR was hypothesized to be predictive. When interpreting this finding, it may be worth considering that venous clots have previously been reported to be fibrin rich (termed white clots) and are known to be a more common cause of flap failure than platelet induced arterial thromboses.[33] However, the notion that fibrin is a more significant factor in venous clots is far from conclusive, and further investigation is needed to elucidate why elevated FPR is associated with flap loss.[34]

Limitations of this systematic review include the heterogeneity of the studies with respect to the type of VET used, VET parameters reported, and anticoagulation protocols, or lack thereof. The timing of blood sample collection also differed between the studies. Moreover, only two of the studies were performed in a prospective manner, and there were no randomized controlled studies found in our search.

CONCLUSIONS

At this time, no firm conclusion can be drawn from this limited data. Viscoelastic parameters relating to the clot strength demonstrate some utility in predicting microvascular thrombotic events, although it is unclear why this may be more useful than other viscoelastic parameters. VET is cheap, fast, and has demonstrated utility in many other surgical applications, which supports continued research efforts. Future studies should standardize study design, anticoagulation, and data reporting to reduce confounding variables. Prospective studies, including randomized controlled trials, will be key to evaluate the prognostic value of viscoelastic tests in microsurgery.

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