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Cardiac shock wave therapy: an alternative non-invasive therapy for refractory angina

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Abstract. – OBJECTIVE: Refractory angina (RFA), known as "no option angina" before, is increasing worldwide. The prognosis for RFA patients still remains poor due to the lack of effective treatments. The potential of cardiac shock wave therapy (CSWT) to treat RFA by promoting angiogenesis was first shown by Nishida et al in a porcine model of chronic ischemic cardiomyopathy. The main objective of this paper is to review the mechanisms of its action, influence on the cardiac tissue, and also clinical studies demonstrating its efficacy.

MATERIALS AND METHODS: This is a literature review of recent articles published on MEDLINE and SciELO databases in English.

RESULTS: Researchers found that CSWT leads to multiple biochemical effects, such as angiogenesis, inflammatory response modulation, ameliorate myocardial fibrosis, and so on. Based on the promising results above, a series of clinical studies have been performed. And the studies demonstrated that CSWT is associated with the improvement of angina symptoms, heart function, and myocardial perfusion for patients with refractory angina. No procedural complications or adverse effects were noted in these studies.

CONCLUSIONS: CSWT appears to be an effective, safe, and non-invasive approach to treat RFA.

Key Words:
Non-invasive, Shock Wave, Refractory angina.

Introduction

Although the current management of ischemic heart diseases has been advanced, numerous patients remain symptomatic. The concept of refractory angina (RFA) has been put forward to describe these patients centuries ago[1]. According to the guideline of Canadian Cardiovascular Society (CCS) in 2012, RFA was defined as "a persistent, painful condition which cannot be controlled by a combination of medication, angioplasty/percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG)" and "the myocardial ischemia must be clinically established to be the root cause"[2]. RFA patients suffer with psychological distress, activity restriction, and impaired health-related quality of life[3]. Meanwhile, the incidence and prevalence of RFA is increasing with the improving coronary artery disease (CAD) related survival rate and the aging society[4]. It is therefore crucial to develop effective therapeutic strategies for RFA patients.

Transmyocardial laser revascularization (TMLR), the mostly studied alternative therapy, is associated with significant early postoperative mortality risk[5]. Other invasive therapies like percutaneous laser revascularization (PMLR) and spinal cord stimulation (SCS) are not suitable for every RFA patient (because of the complications)[6-9]. Enhanced external counter-pulsation (EECP) is a noninvasive therapy that improves symptoms by its hemodynamic effect and has numerous contraindications, such as arrhythmias, peripheral vascular disease, and bleeding diathesis, which occurs commonly in patients with RFA[10,11]. Emerging therapies such as coronary sinus reduction and myocardial cryotherapy are limited by their complicated operation procedure[12,13].

Consequently, cardiac shock wave therapy (CSWT), an application of therapeutic ultrasound, has advanced to eliminate such shortcomings. In this paper, we will review the mechanisms of CSWT, the influence on the cardiac tissue, and clinical studies demonstrating its efficacy. Furthermore, we will discuss the advantages of CSWT and areas in which future research is needed.

Materials and Methods

Mechanisms

Although CSWT has been proven to be effective in preliminary clinical research[14], the precise biomechanical effects of CSWT and its

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therapeutic mechanisms remain obscure. When a mismatch arises between myocardial oxygen needs and myocardial oxygen supply, ischemia, inflammation, cell apoptosis/necrosis, and cardiac remodeling can manifest in succession. CSWT may influence these processes, improving prognosis of RFA. When a shock wave (SW) with relatively high acoustic amplitude (up to about 100MPa) hits tissue, acoustic cavitation and a violent collapse of small gas bubbles in the blood via transmission of SW energy generates localized shear stress on cell membranes[15,16]. This procedure leads to positive biochemical effects, such as up-regulation of vascular endothelial growth factor (VEGF), activation of Toll-like receptor 3 (TLR3) pathway, and so on[17-20]. These effects are described below (Figure 1).

Vascular Permeability

Vascular permeability increasing, the first step of angiogenesis, allows for extravasation of plasma proteins, which lays down a provisional scaffolding for migrating endothelial cells. When Shock wave (SW) hits cells, permeability may also be enhanced by the expanding and compressing ultrasound-activated micro-bubbles[21]. Meanwhile, the endothelial cell-specific receptor, Tie-2 mRNA, is highly increased in the endothelial cells[20]. It indicates that the angiopoietin/Tie-2 system, are involved in CSWT-induced angiogenesis (the system contains angiopoietin 1 that protects cells from excessive vascular leakage and angiopoietin 2 that inhibits Tie2 signaling).

VEGF

VEGF has been proven to be essential in the initiation of angiogenesis[22]. A relative study demonstrated the mRNA expression and the protein levels of fms-like tyrosine kinase (Flt-1) and foetal liver kinase-1(Flk-1) were up-regulated in HUVECs as well as direct VEGF receptors (VEGFR) stimulation. This then leads to the phosphorylation of VEGFR and downstream effects[23,24]. In this study, quantification of relative VEGFR phosphorylation revealed a two-fold increase in VEGFR1 and a nearly four-fold increase in VEGFR2 compared to untreated controls. And SW treatment induced VEGF expression in endothelial cells in a hypoxia-induced factor 1-independent manner. The conclusion that CSWT could enhance angiogenesis by up-regulating of VEGF and its receptors also has recently been suggested in some *in vivo* experiments[17,23,25].

PlGF

Placental growth factor (PlGF) could amplify the angiogenesis effect of VEGF by increasing the responsiveness of VEGFR2 to VEGF and inducing further VEGF release. Zimpfer et al[26] have shown that higher protein levels of PlGF could be found in HUVECs and the extracellular

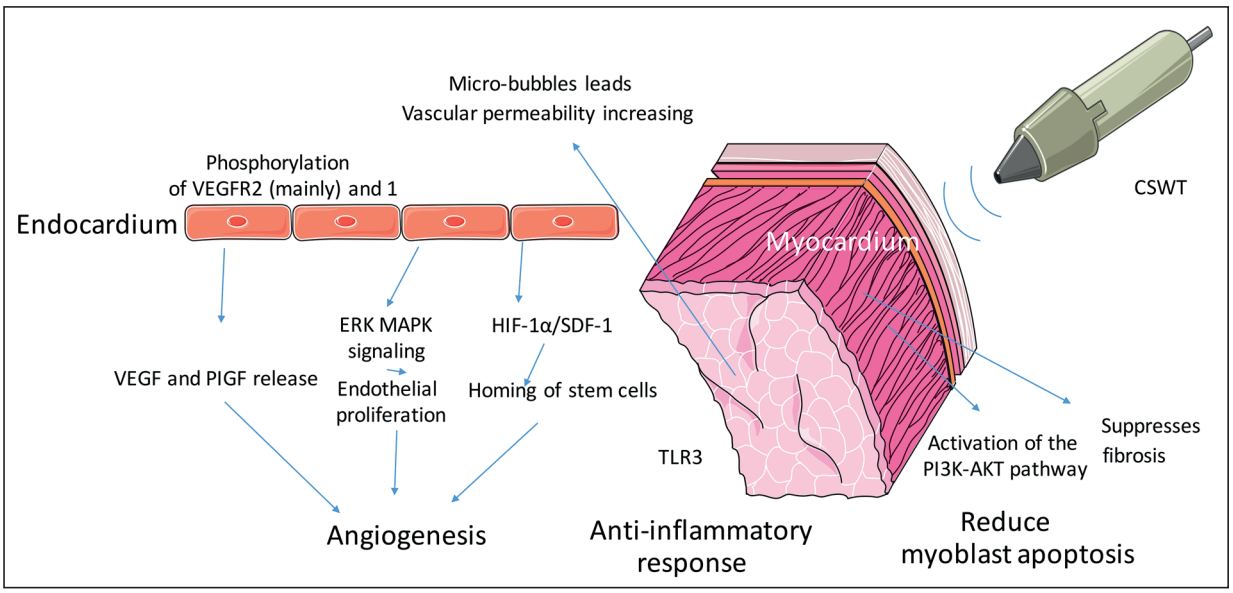

Figure 1. Mechanism of CSWT.

matrix after Shock wave treatment. In addition, Holfeld et al[23] verified that PlGF mRNA was highly up-regulated in SW-treated mice myocardium *in vivo*.

Endothelial Cell Proliferation and Differentiation

Endothelial cell proliferation and differentiation play key roles in angiogenesis. Scholars have confirmed that SW have positive influence on the proliferation and differentiation of cardiomyocytes, smooth muscle, and endothelial cells precursors[27]. Researchers also found that the proliferation of HUVECs is associated with high level of extracellular signal-regulated kinase (ERK). And the significant increase in phosphorylation of extracellular signal-regulated kinase (ERK) after SW treatment can then be suppressed by anti-VEGF neutralizing antibodies[19]. The results indicate that the positive influence may rely on VEGF/ERK/MAPK (mitogen-activated protein kinase) pathway.

Inflammation

Inflammatory processes play an important role in ischemic myocardial pathophysiology. Excessive inflammatory response will hinder the initiation of angiogenesis, while a deficient inflammatory response will disturb the process of replacing necrotic tissue. SW treatment modulates inflammation via the Toll-like receptor 3 (TLR3) pathway. TLR3 activation is characterized by an early pro-inflammatory phase and a late anti-inflammatory response. The interaction between interleukin (IL)-6 and IL-10 in TLR3 stimulation can be schematically seen as a time dependent three-phase regulation. The resulting effect of TLR3 activation may be dependent on the underlying pathologic condition in which it modulates inflammation. This mechanism creates a beneficial environment for angiogenesis in ischemic tissue[28].

Authors have also found that blood perfusion was restored after exposure of SW, and the effect was abolished in TLR3 knockout mice. Furthermore, TLR3 stimulation was impaired when the researchers added RNase in SW-treated HUVECs, while inhibition of protein biosynthesis did not abolish the observed effects. Thus, we could infer that TLR3 cellular RNA mediates the effect of ameliorating blood perfusion[20].

Cell Apoptosis

Once assembled in new vessels, endothelial cells life span become a major problem in the promotion of angiogenesis. Endothelial apoptosis is a natural mechanism and prominent inhibitor of angiogenesis[29]. An *in vitro* study[30] demonstrated that apoptosis could be induced by ischemia/hypoxia in H9c2 cells, and CSWT suppresses the expression of apoptosis molecules by activating of the PI3K (Phosphoinositide 3-kinase)-AKT (Protein kinase B) pathway. Fas/FasL is an important signaling pathway that induces myocardial cell apoptosis that may related to CSWT[31]. However, the effects of CSWT *in vivo* require future investigations.

Endothelial Progenitor Cell Homing

Regenerative medicine has applied in ischemic heart disease increasingly[32]. Based on the previous discovery that there is enhanced recruitment of intravenously injected endogenous endothelial progenitor cells (EPCs) to shock wave-treated ischemic hind limbs in rats[33], Tepekoylu et al[34] found expression of hypoxia-inducible factor 1α (HIF-1α) regulating stromal cell-derived factor-1 (SDF-1) significantly elevated after SW therapy. SDF-1 serves as a chemo-attractants for recruitment of EPCs from bone marrow, and HIF-1α plays a crucial role in the regulation of SDF-1. In line with this finding, significantly greater numbers of proliferating endothelial cells were found in the treatment group[35]. Di Meglio et al[18] confirmed the conclusion that SW facilitates recruitment of endothelial progenitor cells *in vivo*. Zhang et al[36] found that TGF-β1 regulates the SDF-1/CXCR4 axis-induced cells homing in injured myocardial.

Fibrosis of Myocardium

Fibrosis, in general, is a scarring process that is characterized by fibroblast accumulation and excess deposition of extracellular matrix, which leads to distorted organ architecture and function[37]. Numerous studies[18,38] have demonstrated the CSWT could ameliorate myocardial fibrosis. Lei et al[39] found the amount of collagen and CD34/α-smooth muscle actin (αSMA) decreased after SW treatment, and fibrocytes are known to express CD34/αSMA. They hypothesized that CSWT ameliorates myocardial fibrosis by decreasing the amount of fibrocytes. However, the clear mechanism remains to be elucidated.

Activation of Mechanosensors

Due to the developing of the new branch of science named Mechanobiology, researchers began to analyze in details the effects of the physical

stimulus to correlate the interactions of physical energies with the various cell elements[40]. The CSWT also act as pure physical energy to activate a series of cellular events, which supported by some "mechanotransduction pathways". Kazuaki et al[41] demonstrated that caveolin-1 and β1-integrin and its downstream pathways (such as subsequent phosphorylation of Erk and Akt), which could be activated by CSWT, play pivotal roles in the upregulation of angiogenic factors like VEFG. Johannes et al[20] found mechanotransduction of SWT could mediate angiogenesis by releasing of cytoplasmic RNAs of Toll-like receptor 3. We believe the exact mechanism of how the mechanical stimulus from CSWT is translated into a biological response will more clearly in the future. In conclusion, CSWT may lead to positive biochemical effects and improvements in the prognosis of RFA patients by promoting angiogenesis, regulating the inflammatory response, and inhibiting apoptosis and fibrosis. However, more studies are needed to elucidate the mechanism of CSWT in human body.

Clinical Research

Preliminary experimental mechanism works and *in-vivo* animal studies have demonstrated that CSWT may induce a cavitation effect and contribute to angina alleviation by promoting angiogenesis and revascularization in ischemic myocardium. Based on the promising results above, CSWT has been adapted to humans. The first published study of CSWT in patients with end-stage CAD was reported by Fukumoto et al in 2006[42], who indicated that angiogenesis was effectively induced locally at microvascular levels in the targeted ischemic myocardium. Significant clinical improvements (mean CCS class score from 2.7 to 1.8, $p<0.05$) were found after CSWT, correlating with improved myocardial perfusion assessed by stress thallium scintigraphy. Subsequent randomized controlled trials and prospective cohort studies have since demonstrated that RFA patients who underwent 3-month CSWT had a 25-50% reduction in CCS class score[43,44], a 23%-51% reduction in New York Heart Association(NYHA) class[43-46], a 50-100% reduction in nitroglycerin usage[44-48], a 13-41% improvement in 6-min walking test[45-47], and also a slight improvement 6-12% in left ventricular ejection fraction (LVEF)[43,45,47] as compared to the baseline data, which is non-significant in the placebo groups. Wang et al[14] reviewed the results of 14 researches published between 2010 and 2014 including 516 patients in total. Although there was significant heterogeneity across the studies, they found that CSWT improves the angina pectoris symptom, leads to reduce in heart failure (New York Heart Association functional class [-0.49 (-0.62, -0.37), $p < 0.00001$] and improves myocardial viability (improving in total score of perfusion imaging [-5.19 (-8.08, -2.30), $p = 0.0004$] and metabolism imaging [-5.33 (-7.77, -2.90), $p < 0.0001$]).

Treatment Protocols

Numerous clinical trials have confirmed the early beneficial effects from initiation of therapy, as well as sustained positive effects with long-term treatment (Table I). The treatment protocols were devised in a similar schedule in most studies. About 200-300 impulses were applied to the ischemic area using an energy flux density level of 0.09 mJ/mm^2 (adjustable between 0.03 and 0.2 mJ/mm^2) during each session. The session was repeated on days 1, 3, and 5 of the first week in each month. The treatment consisted of 3 sessions in 1 month for totally 3 mouths. The shock waves were targeted on ischemic areas and applied during diastole, while ECG monitoring with R-wave triggering was necessary to avoid inducing ventricular arrhythmias. Wang et al[46] proposed a modified CSWT schedule, in which patients underwent 3 sessions per week, with the 9 total sessions completed in 1 month. Although there was a visible increase in myocardial perfusion imaging (MPI) scores in the 1-month frequent regimen compared to standard 3-month regimen group, the difference is not significant between the two groups. These findings suggest a more frequent regimen probably provides equivalent therapeutic efficacy compared to the 3-month regimen. However, a longer follow-up period should be considered to reach this conclusion.

Clinical Efficacy

While the clinical trials have reached a consensus with the significant improvement in angina symptoms after CSWT, the effect of exercise tolerance and myocardial perfusion have remained in dispute. Most studies demonstrated that CSWT could improve targeted myocardial viability. Resting and dobutamine stress myocardial perfusion imaging (MPI) and echocardiography were used to evaluate the myocardial perfusion and systolic function after CSWT. Kazmi et al[43] found improvements in the size, severity, and nature of ischemia assessed by ^{99m}Tc-MIBI-gated SPECT. Also after CSWT a 75% increase of MPI

Table I. Summary of clinical studies.

Ref. (year)	Trial type	Treatment/ placebo (n)	CCS class	NYHA class	SAQ score	Nitroglycerin use (/week)	LVEF (%)	6-min walk test (m)	Exercise tolerance
Fukumoto et al[42]	Single arm	9	↓**	N/A	N/A	↓**	N/A	↑*	↑=
Kikuchi et al[47]	RCT	4/4	↓**	N/A	N/A	↓**	↑*	↑**	↑=
Wang et al[50]	Single arm	9	↓*	↓=	↑=	↓*	N/A	↑=	N/A
Yang et al[45]	RCT	14/11	↓*	↓*	↑*	↓*	↑*	↑*	N/A
Wang et al[46]	RCT	21(41)/14[§]	↓**	↓*	↑**	↓*	N/A	↑*	N/A
Kazmi et al[43]	PCT	43/43	↓**	↓**	N/A	N/A	↑**	N/A	↑**
Schmid et al[49]	RCT	11/10	N/A	N/A	↑*	N/A	N/A	N/A	↑*
Alunni et al44	PCT	43/29	↓**	↓**	N/A	↓*	N/A	N/A	N/A
Kallerm et al[51]	Single arm	21	↓*	N/A	N/A	N/A	↓=	N/A	↑=
Nirala et al[48]	RCT	41/11	↓*	↓**	↑**	↓*	N/A	↑=	N/A

↑*Increase, statistically significant change in endpoints at baseline and follow-up after CSWT, $p < 0.05$; ↑**Increase, statistically significant, $p < 0.01$; ↑=Increase, non-significant. ↓=Decrease, statistically significant, $p < 0.05$; ↓**Decrease, statistically significant, $p < 0.01$; ↓=Decrease, non-significant; N/A Not applicable. [§]20 of 41 patients who received modified one-month CSWT regimen were not included. CCS Canadian Cardiovascular Society functional classification of angina; NYHA New York Heart Association Functional Classification; LVEF left ventricular ejection fraction; SAQ Seattle Angina Questionnaire; PCT prospective cohort study; RCT randomized controlled trial.

score and a 28% increase of peak systolic strain rate (PSSR) were reported in a randomized controlled trial[46]. Nevertheless, one study failed to show significant improvement in myocardial perfusion[49]. MPI and PSSR indicated no significant difference in 9 patients at rest or under low-dose dobutamine stimulation[50]. Thus, treatment of the targeted ischemic area seems to be beneficial with respect to the CCS score, although no significant changes in global myocardial perfusion are observed, which demonstrated by the maximum exercise capacity test, indicating that no significant change in exercise tolerance occurred during the follow-up period[47,50,51]. The undesired global myocardial perfusion results indicate that a local noninvasive regimen may not significantly improve advanced stage disease. The underlying long-term prognosis and mortality improvement of RAF is questioned after CSWT. The unfavorable results, however, may be attributable to the small sample size and relatively short follow-up period. Also, long-term morbidity and mortality in patients with RFA is lower than previously reported[3]. Thus, therapeutic options could focus on the angina relief and improved quality of life which is promisingly noted in CSWT investigatons.

Safety

It is important to note that CSWT is safe and well tolerated in clinical practice. Wang et al[46] found that isolated premature ventricular contraction (PVC) occurred in 6 of 41 cases during CSWT, but did not result in patient discomfort or change in patient blood pressure, heart rate, or oxygen saturation. Of note, subsequent PVCs did not occur during the follow-up period. Several patients reported mild chest pain when the wave energy was increased during CSWT but was relieved soon after the energy was reduced[45,46]. Still, there is a theoretical concern that exposure of shock wave could lead to plaque rupture, induce apoptosis, or damage endothelium. However, serial measurement of cardiac biomarkers after CSWT showed no changes compared with the placebo group[45]. Kaller et al[51] demonstrated a significant increase of perfusion in targeted myocardial segments, whereas no change occurred in the remote segments. Thus, CSWT can precisely target locations of ischemic myocardium, and the current study also confirms that none of patients suffered from procedural complications, arrhythmias, pericardial disease, heart failure, or skin damage.

There was only one research[48] described the long-term outcomes of CSWT. Nirala et al[48] enrolled 52 patients with 41 patients in shock wave group. Following 6 years of follow-up, they found that there is no adverse effect in shock wave group and the CSWT improved myocardial function and quality of life in RFA patients.

However, there is still a lack of evidence from reliable, large-scale clinical trials with CSWT. More assessment of long-term effect on quality of life in multi-center randomized studies should be considered.

Discussion

The prognosis for RFA patients remains poor due to the lack of effective treatment options. The emerging therapies have their own disadvantages, which limit their clinical use. For example, bone marrow cell transplantation therapy, dependents on adult stem cell plasticity, may also be a useful strategy for angiogenesis. Endothelial progenitor cells can be isolated from circulating mononuclear cells in humans and have been shown to be incorporated into neovascularization[52]. However, the need for invasive delivery of those cells to the ischemic myocardium may severely limit the clinical use.

Extracorporeal shock wave therapy (ESWT) was first applied in patients in 1980 to break up kidney stones[53]. ESWT is currently approved by the United States Food and Drug Administration (FDA) for the treatment of solid tumors, uterine fibroids, glaucoma, kidney stones, deep venous thrombosis, and musculoskeletal injuries[54,55]. The novel findings present studies demonstrate that the extracorporeal CSWT normalizes myocardial function in RFA patients. Compared to the emerging therapies, mostly invasive in nature and with unestablished safety margins, a major advantage of CSWT over various emerging therapies is shown by the fact that it is quite non-invasive and safe, with minimal procedural complications or adverse effects. If necessary, CSWT could be used repeatedly treat in- or outpatients due to the fact no surgery, anesthesia, or even catheter intervention is required for the treatment. This is an important factor in determining the clinical usefulness of angiogenic therapies in elderly patients with RFA (Table II).

However, most of current studies concerned with the mechanism of CSWT were *in vitro*, and the physical characteristics of the shock waves applied *in vitro* are not comparable with those present during an extracorporeal cardiac shock wave treatment. The presence of liquid-air interface in the cell culture dish induces the reflec-

Table II. Comparative outcomes of different therapy.

	Invasiveness	Operation complexity	Initial year	Costs	Release symptoms	Improve prognosis	Disadvantages
TMLR	+++	+++	1980s	High	+	-	High early mortality
PMLR	++	++	1990s	High	+	-	Myocardial perforation and other severe complications
SCS	+	++	1997	Similar to CABG	+	+	Not suitable for patients with spinal diseases
EECP	-	+	1999	Low	+	N/A	Contraindicated for persons with arrhythmias uncontrolled congestive heart failure et al
CSR	+	++	2007	Similar to CABG	+	-	Several complications may occur; research is far from sufficient
MCT	+	++	2003	Similar to PCI	+	N/A	Only two studies with 21 cases existed; safety is unclear
CSWT	-	+	2006	Low	+	N/A	Little risk of arrhythmia; long term effects is unclear

TMLR: Transmyocardial laser revascularization, PMLR: percutaneous laser revascularization, SCS: spinal cord stimulation, EECP: enhanced external counter-pulsation, CSR: Coronary sinus reducer, MCT: Myocardial cryotherapy, CSWT: Cardiac shock wave therapy, CABG: artery bypass grafting, PCI: percutaneous coronary intervention.

tion of shock waves, which then interferes with the primary wave form. This does not occur in human tissue *in vivo*. Thus, more *in vivo* experiments are needed in the future.

In addition, there are no large, randomized clinical trials of CSWT for RFA. So, although we could deduce that there are no long-term adverse effects of CSWT according to its mechanism, the complication and long-term prognosis of RFA patients treated with CSWT still requires further evaluation.

Conclusions

Overall, CSWT appears to be an effective, safe, and non-invasive approach to ameliorate myocardial ischemia in patients with RFA, without procedural complications or adverse effects. The beneficial effects of CSWT may rely on angiogenesis, modulation of the inflammation response, depression of apoptosis, and amelioration of myocardial fibrosis. Although more mechanical experiments in human body and large-scale clinical trials are needed, CSWT remains a promising alternative therapy for refractory angina.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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