Reduced effects of cardiac extracorporeal shock wave therapy on angiogenesis and myocardial function recovery in patients with end-stage coronary artery and renal diseases

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\textbf{A B S T R A C T}

Background: Growing evidence have shown cardiac extracorporeal shock wave therapy (ESWT) improve clinical symptoms and left ventricular ejection fraction (LVEF) for patients with end-stage diffuse coronary artery disease (EnD-CAD) unsuitable for coronary interventions. However, little is known whether cardiac ESWT remains effective on symptomatic relief and improvement of LVEF for the EnD-CAD patients with end-stage renal disease (ESRD).

Methods: This was a small-scale prospective study. Between August 2016 and January 2019, a total of 16 subjects received cardiac ESWT for their EnD-CAD. They were divided into two groups according to ESRD or not, i.e., EnD-CAD group (n = 8) and EnD-CAD/ESRD group (n = 8). Clinical symptoms including angina and dyspnea, levels of circulating endothelial progenitor cells (EPC), LVEF, and adverse events were regularly followed up for one year to compare safety and efficacy of cardiac ESWT between the EnD-CAD patients with or without ESRD.
Results: All participants tolerated cardiac ESWT without any relevant side effects such as skin allergic reaction, local redness/tenderness or cardiac arrhythmia. There were similar baseline comorbidities and clinical features between two groups, but the EnD-CAD/ESRD group had significantly higher serum potassium level as well as lower renal function and lipid profile (all \(p\)-values <0.03). After cardiac ESWT, the patients in both groups had significant improvement in angina and dyspnea at 1 year (all \(p\)-values <0.03). However, the EnD-CAD/ESRD group did not have increase in either circulating EPC levels or LVEF at 6 months (mean change in LVEF: -4.00% ± 8.32%, \(p = 1.000\)). In contrast, the EnD-CAD group had gradually improving levels of circulating EPC surface markers and increased LV systolic function (mean change in LVEF: +4.87% ± 8.76%, \(p = 0.092\)). Notably, patients in the EnD-CAD/ESRD group suffered from high incidental clinical adverse events before and after enrollment into the ESWT study (75% vs. 25%, \(p = 0.132\)).

Conclusion: Although cardiac ESWT provided improvement of clinical symptoms in the EnD-CAD patients, its long-term effects on the angiogenesis and LVEF were reduced for those high-risk patients with concomitant EnD-CAD and ESRD.

Trial registration: none.

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of death worldwide with a growing incidence, according for more than 15 million global deaths annually [1]. Of them, although diffuse coronary artery disease (CAD) occurred in less than 5% of ASCVD [2], it has significantly higher risk for heart failure or sudden cardiac death compared with single or multiple vessel CAD [3,4]. Patients with ASCVD usually have multiple vascular involvement and comorbidities due to sharing common atherosclerotic risk factors and pathology of chronic systemic inflammation [5,6]. Kidney involvement was usually observed in patients with diffuse CAD [7], especially for those with poorly controlled diabetes [8]. Unfortunately, even with efforts in treating and preventing progression of chronic kidney disease (CKD), a part of patients with CAD and CKD eventually developed end-stage renal disease (ESRD), leading to substantially high rates of morbidity and mortality [9].

Clinical observational studies have revealed around 15–20% of patients with CAD were afflicted with severe and diffuse atherosclerotic obstructive coronary lesions unsuitable for percutaneous or surgical coronary intervention [10,11]. Currently, aside from anti-ischemic medical therapy [12], more and more therapeutic strategies such as enhance extracorporeal counter pulsation (ECCP) therapy [13], cell-based therapy [14] and cardiac extracorporeal shock wave therapy (ESWT) [15,16] have been utilized for treatment of the so-called end-stage diffuse CAD (EnD-CAD). Although there are relatively small cohorts in the aforementioned studies [13–16], these abovementioned alternative therapies alleviate refractory angina and increase coronary circulation through upregulating expression of vascular endothelial growth factor (VEGF) and enhancing angiogenesis [17]. Compared to cell-based therapy which needs time for cell preparation and invasive procedure for delivering cell production into target myocardium [18,19], low-energy cardiac ESWT possesses convenient, time-saving, and non-invasive advantages [15,16,20,21]. Nevertheless, because ESRD patients were excluded from majority of ESWT studies, little is known regarding whether cardiac ESWT is also effective for patients with simultaneous EnD-CAD and ESRD. In this study, we aimed to compare the effect of cardiac ESWT on clinical and laboratory outcomes between the high-risk EnD-CAD patients with and without ESRD.

Materials and methods

Study ethics, design, and objective

The study was approved by the Institutional Review Committee on Human Research at Chang Gung Memorial Hospital (101–3758A3, 201600349A3-C501/C502/C601) in June 2016.
supported by a program grant from Chang Gung Memorial Hospital and Chang Gung University (grant numbers: CRRPG8F0511 [1/3], CRRPG8F0512 [2/3], CRRPG8F0513 [3/3]), and conducted at Kaohsiung Chang Gung Memorial Hospital, a tertiary medical center. This was a single-center prospective study to test the safety and efficacy of cardiac ESWT in the patients with concomitant EnD-CAD and ESRD. The EnD-CAD was defined as diffuse diseased lesions longer than 20 mm over than two major epicardial coronary arteries on coronary angiography. Myocardial revascularization therapy was considered infeasible for dealing with EnD-CAD after heart-team evaluation. End-stage renal disease was defined as estimated glomerular filtration rate (eGFR) less than 15 ml/min/1.73 m² for more than 3 months regardless of dialysis.

Outcome measures

The primary endpoints were to investigate safety and the improvement in clinical symptoms including angina and dyspnea. The safety was evaluated according to adverse clinical events such as arrhythmia or dynamic ST-T changes on electrocardiography (ECG) during and after cardiac ESWT. The angina was graded with Canadian Cardiovascular Society (CCS) Angina Score and dyspnea was assessed by New York Heart Association Functional Class (NYHA Fc) at baseline and every 3 months. Secondary endpoints included 1) one-year all-cause mortality rate and major adverse cardiac and cerebrovascular events (MACCE, defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke); 2) changes of left ventricular ejection fraction (LVEF) on echocardiography between baseline and 6 months after cardiac ESWT; and 3) serial changes of circulating endothelial progenitor cell (EPC) level.

Calculation of rational sample size for secondary endpoints

According to our previous publication of cell-based therapy for EnD-CAD [19], the mean change in the improvement of LVEF between baseline and 1-year follow-up echocardiography in study and control group was 6% ± 3% and 2% ± 3%, respectively. Therefore, an estimated sample size of 10 patients in each group was calculated on the basis of an effect size of 1.33 with two tails, α = 0.05, power of 80%, and assumed 5.0% rate of protocol violations and incomplete follow-up.

Eligibility, inclusion and exclusion criteria

Patients aged between 20 and 80 years who had ESRD and obstructive CAD with coronary angiographic findings of at least two severe diffuse CAD were included in this study. They were considered as noncandidates for coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) after heart team approach. They presented with CCS grade II-IV angina, and were found to have reversible myocardial ischemia shown on thallium 201 myocardial perfusion scan. In addition, patients with history of previous PCI or CABG were allowed to be enrolled if they had unsuitable lesions for further intervention. In contrast, patients with the following history or conditions were excluded: age <20 or >80 years, major surgery or trauma in recent 3 months, acute myocardial infarction Killip class III or IV, acute decompensated heart failure with respiratory or circulatory instability, liver cirrhosis, active hematologic or autoimmune disorders, malignancy, acute or chronic inflammatory disease at study enrollment, severe valvular heart disease, life expectancy less than one year, or pregnant women.

From August 2016 to January 2019, we consecutively enrolled a total of 11 patients with EnD-CAD and ESRD after excluding 7 cases of screen failure owing to surgical revascularization considered possible for severe diffuse CAD after heart team discussion. Eight patients successfully received cardiac ESWT. The remaining three cases were withdrawn because of recurrent sepsis and newly diagnosed malignancies during waiting for ESWT. Considering hard to enroll such kind of high-risk and fragile EnD-CAD/ESRD patients, we did not allocate them into sham-control group who just received standard medical therapy. Instead, we enrolled 8 patients diagnosed with EnD-CAD but without ESRD as comparison group. We provided the therapeutic choice to the candidates with EnD-CAD alone and enrolled them into the current study if they agreed to receive cardiac shock wave as an alternative therapy for their severe diffuse CAD unsuitable for any coronary intervention. The purpose was to investigate the therapeutic effect of cardiac ESWT on the improvement of clinical outcome and cardiac functions between EnD-CAD with and without ESRD. The detailed protocol for the patients’ enrollment, allocation and follow-up was displayed in [Supplemental Fig. 1]. Additionally, the echocardiographer, technicians, clinical nurses and physicians who cared the patients in inpatient or outpatient setting were blinded to the study design and allocation. Only the cardiologists responsible for heart-team discussion and performing cardiac ESWT were unblinded to the study.

Procedure and protocol of cardiac ESWT

The procedure of cardiac ESWT was performed according to manufacturer’s instruction using Cardiospec™ (Medispec Ltd, Gaithersburg, MD, USA) which was designed for extracorporeal shock wave (SW) myocardial revascularization [22]. In detail, patients in both groups were positioned on the table and connected to the ECG monitor. The target area and location of ischemic myocardium were based on the findings of thallium scan. The treated area was divided into 1 × 1 cm² zones with 100 shocks/zone under echocardiographic guidance for three different courses. Every shock was gated with ECG to avoid ectopic arrhythmia during SW therapy. Ultrasound gel was smeared on the SW applicator membrane and on the skin of patient’s chest wall for reducing energy loss. Cardiac ESWT was then performed with the application of 100 shocks/spot at 0.09 mJ/mm² energy flux density for at least 8–10 spots each time, three times a week, and at weeks 1, 5 and 9. It needed around 9 weeks to complete a total of 9-course cardiac ESWT.

During and after each SW treatment session, patients were evaluated for cardiac symptoms, ECG abnormalities, adverse events and complications. Any event would be recorded in a case profile by research assistant or technician. Cardiac troponin I was not routinely checked unless the patients presented with cardiac arrhythmia or chest discomfort during

\[ e_{\text{GFR}} = \frac{\text{eGFR}}{10} \]
SW procedure. The concentration of cardiac troponin I (normal range: <0.5 ng/mL) was measured by standard method in the Department of Clinical Biochemistry and Pathology of our hospital.

Flow cytometric assessment of circulating EPC levels

The procedure and protocol have been described in our previous study [19]. In detail, EPC populations in circulation were identified by flow cytometry using double staining through fluorescence-activated cell sorter (FACSCalibur™ system; Beckman Coulter Inc, Brea, CA, USA). Each analysis included 300,000 cells per sample. The assays for circulating EPCs in each sample were performed in duplicate and mean levels were reported. Intra-assay variability based on repeated measurement of the same blood sample was low with a mean coefficient of variance of 3.9% among the study subjects. Blood samples were drawn for flow cytometric analysis at baseline before cardiac ESWT and at 1, 3, and 6 months after completion of SW therapy.

Medications

Patient’s standard regimen were not changed before and during cardiac ESWT unless discomfort was complained. Aspirin was the first choice for all patients unless they were allergic or intolerant to aspirin. If so, P2Y12 inhibitor, e.g., clopidogrel or ticagrelor, was prescribed instead. Other cardioprotective or anti-ischemic drugs including statin, beta blocker, renin-angiotensin system (RAS) inhibitor, calcium channel blocker, and coronary vasodilator, were prescribed according to guideline recommendations.

Echocardiographic and clinical follow-ups

The two- and three-dimensional (2D and 3D) transthoracic echocardiography (TTE) were performed by an experienced cardiologist who was blinded to the study allocation. Size of cardiac chambers and left ventricular systolic and diastolic functions were evaluated with TTE at baseline and 6 months after cardiac ESWT, or as needed if the patient suffered from unexpected hospitalization. 3D LVEF was calculated with the formula: (LV end-diastolic volume – LV end-systolic volume)/LV end-diastolic volume. Additionally, left atrial (LA) index was measured with biplane area-length method via apical four and two camber views.

Aside from regular follow-up at our outpatient clinic, a case report file recording all patients’ clinical information was designed for each study subject, and regularly completed by a research nurse after every clinical visiting or rehospitalization, as well as through telephone interviews on an irregular basis.

Statistical analysis

Per-protocol analysis was used in this study. All variables are expressed as mean ± standard deviation or number with percentage as appropriate. For sample size in each group with nonparametric variables, Mann–Whitney U test was performed for comparison of continuous variables between the two groups, including baseline data and outcome assessment. Fisher exact test was utilized to compare difference between two independent categorical variables (n = 8 in each group). Additionally, Wilcoxon sign rank test was applied in the same group to identify the changes of continuous variables between different time points. Statistical analysis was performed using SPSS statistical software for Windows version 19 (SPSS for Windows, version 19; SPSS, IL, USA). A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics [Table 1] and safety of cardiac ESWT

At baseline, there was no difference in clinical features including age, gender, body mass index, atherosclerotic risk factors, comorbidities, and history of revascularization between study and comparison groups, except all patients in the EnD-CAD/ESRD group were on maintenance hemodialysis. More than half of patients in either study or comparison groups had traditional atherosclerotic risk factors such as hypertension, diabetes, and dyslipidemia. Around forty percent of patients in the EnD-CAD group had advanced CKD. All patients in both groups had multiple vessel CAD with more than 80% of left main stem involvement. In addition, majority of them had undergone either CABG or PCI as revascularization strategy.

Regarding laboratory data, the EnD-CAD/ESRD group had significantly higher serum creatinine and potassium and lower eGFR than the EnD-CAD group. On the contrary, lipid profile including total cholesterol and low-density lipoprotein cholesterol were significantly lower in the EnD-CAD/ESRD group than in the EnD-CAD group. The prescribed oral medications did not differ between groups. Cardiac ESWT were all successfully applied to all 16 patients in the EnD-CAD/ESRD and EnD-CAD groups. There was no relevant side effects such as painful sensation and cardiac arrhythmia during SW procedure, as well as ecchymoses or chest discomfort after SW therapy.

Comparison of clinical, laboratory, and echocardiographic outcomes [Table 2 and Fig. 1]

Half one year after cardiac ESWT, patients in the two groups had significant improvement of CCS angina score as compared to baseline presentation. However, EnD-CAD/ESRD patients expressed slower improvement in 6-month NYHA functional class than EnD-CAD counterparts. One year later, cardiac ESWT provided benefit in the improvement of both angina and dyspnea in two groups, although patients with EnD-CAD/ESRD had insignificantly higher scores of angina and dyspnea than those with EnD-CAD only.

Surface markers of circulating EPCs, including CD34 + CD31 + CD45dim, CD34 + KDR + CD45dim and CD34 + CD133 + CD45dim, did not differ between two groups at either baseline or six months after cardiac ESWT [Table 2]. Taking a closer look, there were gradually and significantly improving levels of circulating EPCs in the EnD-CAD group from baseline to six months (p = 0.009, 0.038 and 0.017 for
### Table 1 Baseline characteristics between EnD-CAD patients with and without ESRD.

| Variables                          | EnD-CAD/ESRD Group (N = 8) | EnD-CAD Group (N = 8) | p-value |
|------------------------------------|-----------------------------|------------------------|---------|
| Clinical features                  |                             |                        |         |
| Age, year                          | 69.13 ± 5.19                | 68.88 ± 8.89           | 0.847   |
| Male sex, n (%)                    | 6 (75%)                     | 8 (100%)               | 0.467   |
| Body mass index                    | 23.11 ± 2.47                | 25.44 ± 3.34           | 0.179   |
| Smoker, n (%)                      | 2 (25%)                     | 3 (37.5%)              | 1.000   |
| Hypertension, n (%)                | 8 (100%)                    | 7 (87.5%)              | 1.000   |
| Diabetes mellitus, n (%)           | 7 (87.5%)                   | 7 (87.5%)              | 1.000   |
| Dyslipidemia, n (%)                | 4 (50%)                     | 7 (87.5%)              | 0.282   |
| Gout, n (%)                        | 3 (37.5%)                   | 1 (12.5%)              | 0.569   |
| COPD, n (%)                        | 1 (12.5%)                   | 1 (12.5%)              | 1.000   |
| CKD stage 3–5, n (%)               | 0 (0%)                      | 3 (37.5%)              | 0.200   |
| On hemodialysis, n (%)             | 8 (100%)                    | 0 (0%)                 | <0.001  |
| Old stroke, n (%)                  | 1 (12.5%)                   | 0 (0%)                 | 0.467   |
| Old myocardial infarction, n (%)   | 3 (37.5%)                   | 2 (25%)                | 1.000   |
| Post CABG, n (%)                   | 3 (37.5%)                   | 4 (50%)                | 1.000   |
| Post PCI, n (%)                    | 8 (100%)                    | 5 (62.5%)              | 0.200   |
| History of coronary stenting, n (%)| 7 (87.5%)                   | 5 (62.5%)              | 0.569   |
| Left main involvement, n (%)       | 7 (87.5%)                   | 7 (87.5%)              | 1.000   |
| 2- or 3-vessel CAD, n (%)          | 8 (100%)                    | 4 (50%)                | –       |
| History of heart failure, n (%)    | 1 (12.5%)                   | 4 (50%)                | 0.282   |
| Atrial fibrillation/flutter, n (%) | 2 (25%)                     | 0 (0%)                 | 0.467   |
| Post pacemaker implantation, n (%) | 2 (25%)                     | 0 (0%)                 | 0.467   |
| Peripher al vascular disease, n (%)| 2 (25%)                     | 1 (12.5%)              | 1.000   |

### Table 2 Outcome comparison.

| Variables                          | EnD-CAD/ESRD Group (N = 8) | EnD-CAD Group (N = 8) | p-value |
|------------------------------------|-----------------------------|------------------------|---------|
| Clinical symptoms                  |                             |                        |         |
| CCS angina score at baseline       | 3.88 ± 0.35                 | 4.00 ± 0.00            | 0.317   |
| CCS angina score at 6 months       | 1.71 ± 0.76                 | 1.63 ± 0.52            | 0.896   |
| CCS angina score at 12 months      | 1.67 ± 0.82                 | 1.13 ± 0.35            | 0.122   |
| p-value<sup>12-mo</sup> vs baseline|                             |                        |         |
| NYHA Fc for dyspnea at baseline    | 3.25 ± 0.89                 | 3.38 ± 0.74            | 0.879   |
| NYHA Fc for dyspnea at 6 months    | 2.29 ± 0.95                 | 1.25 ± 0.46            | 0.016   |
| NYHA Fc for dyspnea at 12 months   | 1.50 ± 0.55                 | 1.13 ± 0.35            | 0.139   |
| p-value<sup>12-mo</sup> vs baseline NYHA Fc | 0.026 | 0.010 |

### Echocardiographic findings

| Variables                          | EnD-CAD/ESRD Group (N = 8) | EnD-CAD Group (N = 8) | p-value |
|------------------------------------|-----------------------------|------------------------|---------|
| LA volume index at baseline, mL/m² | 35.00 ± 6.27 | 31.00 ± 8.65 | 0.101   |
| LA volume index at 6 months, mL/m² | 35.57 ± 7.09 | 28.88 ± 4.82 | 0.324   |
| 3D LVEDV at baseline, mL           | 113.43 ± 45.68 | 148.00 ± 20.73 | 0.072   |
| 3D LVEDV at 6 months, mL           | 128.00 ± 41.09 | 134.75 ± 57.06 | 0.862   |
| 3D LVEF at baseline, %             | 55.88 ± 11.54 | 52.38 ± 16.18 | 0.713   |
| 3D LVEF at 6 months, %             | 53.29 ± 18.54 | 57.25 ± 11.94 | 0.862   |
| Change (%) of 3D LVEF<sup>6-mo</sup> vs baseline | -4.00 ± 8.32 | +8.47 ± 8.76 | 0.417   |

| p-value<sup>6-mo</sup> vs baseline LVEF | 1.000 | 0.092 |
| Mean E/E<sub>+</sub> at baseline | 20.50 ± 7.18 | 14.83 ± 8.86 | 0.059   |
| Mean E/E<sub>+</sub> at 6 months | 17.07 ± 6.09 | 15.77 ± 10.85 | 0.325   |

| One-year clinical outcomes         | EnD-CAD/ESRD Group (N = 8) | EnD-CAD Group (N = 8) | p-value |
| Composite endpoints, n (%)         | 6 (75%) | 2 (25%) | 0.132 |
| All-cause mortality, n (%)         | 2 (25%) | 0 (0%)   | 0.467   |
| MACCE, n (%)                       | 4 (50%) | 1 (12.5%) | 0.282   |
| Hospitalization for HF, n (%)      | 2 (25%) | 1 (12.5%) | 1.000   |

Data are expressed as mean ± standard deviation, or n (%). Abbreviations: EnD-CAD: end-stage diffuse coronary artery disease; ESRD: end-stage renal disease; CCS: Canadian cardiovascular society; NYHA Fc: New York Heart Association functional class; EPC: endothelial progenitor cell; LA: left atrial; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MACCE (defined as cardiovascular death, myocardial infarction, or stroke); major adverse cardiac and cerebrovascular events; HF: heart failure.
CD34+CD31+CD45dim, CD34+KDR+CD45dim and CD34+CD133+CD45dim, respectively) [Fig. 1D–E]. In contrast, EnD-CAD/ESRD group expressed fluctuant levels of the three surface markers of circulating EPCs since cardiac ESWT, or even unchanged levels between baseline and six months (p = 0.965, 0.240 and 0.428 for CD34+CD31+CD45dim, CD34+KDR+CD45dim and CD34+CD133+CD45dim, respectively) [Fig. 1A–C], implicating angiogenic effect of cardiac ESWT was suppressed or unstable in the circumstance of ESRD.

The LA size was insignificantly larger and the volume of left ventricle (LV) was insignificantly smaller in the EnD-CAD/ESRD group than in the EnD-CAD group, either at baseline (p = 0.101) or at 6-month follow-up (p = 0.324). The discrepancy in chamber sizes between LA and LV in two groups was supposed to be related to poorer LV compliance in the ESRD and more volume reduction status through regular ultrafiltration of hemodialysis. Additionally, two groups had similar values of LVEF at baseline and six months following cardiac ESWT. Interestingly, compared to increase in 6-month LVEF (+4.87%) after SW therapy in the EnD-CAD group, the 6-month LVEF was decreased (−4.00%) in the EnD-CAD/ESRD group, although the difference did not reach statistical significance. Furthermore, the EnD-CAD/ESRD group had insignificantly poorer diastolic dysfunction including both larger LA volume index and higher mean E/E’ value than the En-D-CAD counterpart at baseline and six months following ESWT.

As shown in the bottom of [Table 2], during one-year follow-up period, the patients in the En-D-CAD/ESRD group experienced much more incidence of adverse clinical outcomes, e.g., death, myocardial infarction and heart failure, than those in the En-D-CAD group.

**High incidence of clinical events in the patients with En-D-CAD/ESRD [Table 3]**

Since enrollment, EnD-CAD/ESRD patients were observed high incidence rate of unpredictable adverse events. Three cases did not have chance to receive SW therapy because of recurrent sepsis and incidental malignancies. Two cases who completed SW therapy died of septic shock and hypoglycemia-related in-hospital cardiac arrest. Four in 8 ESWT cases suffered from MACCE, including two having acute coronary syndrome in need of hospitalization for dual antiplatelet and anticoagulation therapy, one developing bilateral severe peripheral vascular disease status post repeated revascularization therapy, and the other one being hospitalized for heart failure with preserved LV function. Overall, patients with end-stage coronary artery and renal diseases were at risk for any clinical adverse events, suggesting cardiac ESWT might lose its therapeutic role and be unsuitable for such kind of high-risk patient population.

**Discussion**

This prospective case–control study to test whether cardiac ESWT is effective in treating patients with En-D-CAD and ESRD yielded several important findings. Firstly, cardiac ESWT provided significantly symptomatic relief of angina and
dyspnea in the patients having EnD-CAD irrespective of ESRD. Secondly, circulating level of EPCs, an indicator of angiogenesis, was consistently increasing after SW therapy in the EnD-CAD group but fluctuant in the EnD-CAD/ESRD group, suggesting that ESRD was a circumstance unsuitable for cardiac ESWT. Thirdly, cardiac ESWT did not improve LVEF or reverse LA/LV remodeling process in the EnD-CAD patients with ESRD. Lastly, quite a number (9 in 11) of EnD-CAD/ESRD patients suffered from adverse clinical events either on waiting for or after cardiac ESWT, implicating we should take into more consideration whether application of the SW therapy is cost-effective in this kind of high-risk patients.

Previous studies [15,16,20,21] have shown that cardiac ESWT effectively not only releases clinical symptoms but also improves LVEF in patients with severe diffuse CAD and refractory angina. In the present study, for the patients with EnD-CAD only, SW therapy provided benefits in the improvement of angina and dyspnea as well as increment of circulating EPCs and LVEF. Therefore, our findings were compatible with those from the previous researches [15,16,20,21]. Also, cardiac ESWT was found to offer benefits in the symptomatic relief for angina and dyspnea in the patients with EnD-CAD and ESRD, although the improvement was somewhat slower and smaller as compared with those with EnD-CAD only. Thus, this was the first study to observe the positive effect of cardiac ESWT on the angina or dyspnea among the EnD-CAD/ESRD patients. Nevertheless, the result should be interpreted carefully or was considered as placebo effect because this study was not a randomized design. At least, it seems possible and practical to apply this alternative therapeutic strategy, i.e., cardiac ESWT, for the ESRD patients presenting with refractory angina or dyspnea owing to their severely calcified diffuse CAD.

Except for clinical benefit of cardiac ESWT on the symptomatic relief, majority of results in the EnD-CAD/ESRD group demonstrated unfavorable laboratory and clinical outcomes during 1-year follow-up, including unstable levels of circulating EPCs, absence of LA/LV reverse remodeling effect, worsening change of LVEF and higher rate of adverse events. The above findings were supported by a previous review of mesenchymal stem cell therapy in patients with CKD [23], highlighting older age, coexisting cardiovascular disease, diabetes, chronic inflammatory states, and uremia in CKD limits cell functions of pro-angiogenic, anti-inflammatory/fibrotic activity and paracrine effects. On the other hand, we observed a small advantage from cardiac ESWT for EnD-CAD/ESRD in the slight reduction in mean E/E’, indicating SW therapy might improve LV diastolic dysfunction and decrease LA filling pressure. This observation was, at least in part, explained why cardiac ESWT still could provide symptomatic relief for angina and dyspnea among the ESRD patients.

In the current study, patients’ screening was very slow because majority of EnD-CAD/ESRD patients were hospitalized with initial diagnoses of infection/sepsis, decompensated heart failure, or acute coronary syndrome. Study conduction of cardiac ESWT was considered only after disease stabilization and exclusion of fragile patients and noncandidates. Unfortunately, a part of potentially eligible ESRD patients with refractory CAD suffered from another episode of adverse clinical events during hospitalization or after discharge, so they lost chance of further enrollment. Additionally, the enrollment was also very difficult because their CAD, even multi-vessel disease and complex calcified lesions, mostly could be managed with surgical or percutaneous coronary intervention following rotational atherectomy. Furthermore, compared to convenience in application of ESWT for the treatment of neuromuscular diseases [24], the preparation and execution of cardiac ESWT for either refractory CAD or heart failure was rather complex (localization of ischemic regions), time-consuming (EKG-gated), and expensive (around 600 US dollars for one case) [25]. Hence, in light of the EnD-CAD/ESRD patients having much higher incidental clinical adverse events such as sepsis, malignancy and MACCE, we should take cost-effectiveness of cardiac ESWT for ESRD population into account and think about more whether it deserves to perform a randomized placebo-control trial in the future.

### Table 3: High risk for adverse events among patients with EnD-CAD and ESRD since enrollment.

| Case No. | Age/Sex | ESWT | Cause of withdrawal or clinical adverse events |
|----------|---------|------|-----------------------------------------------|
| W01      | 54/M    | No   | Diagnosis of hepatocellular carcinoma 2 mo after enrollment |
| W02      | 70/M    | No   | Recurrent hospitalizations for severe sepsis resulted from lung empyema, cholecystitis, and intra-abdominal infection during waiting for ESWT |
| W03      | 62/F    | No   | Diagnosis of antiphospholipid antibody syndrome and bladder cancer 3 mo after enrollment, development of deep venous thrombosis |
| Case 01  | 65/M    | Yes  | Hospitalization for acute decompensated heart failure and HFpEF 9 mo after ESWT |
| Case 02  | 61/F    | Yes  | Expired due to pneumonia with respiratory failure and septic shock 10 mo after ESWT |
| Case 03  | 76/M    | Yes  | NSTE-ACS s/p balloon angioplasty at culprit LAD at 9 mo after ESWT |
| Case 04  | 69/M    | Yes  | Bilateral PVD with chronic unhealed ulcers status post repeated PTA 6 mo after ESWT |
| Case 05  | 67/M    | Yes  | Recurrent unstable angina since 10 mo after ESWT |
| Case 06  | 73/F    | Yes  | In-hospital cardiac arrest owing to hypoglycemia and heart attack 8 mo after ESWT |
| Case 07  | 67/M    | Yes  | None (stable condition during 1-year follow-up) |
| Case 08  | 75/M    | Yes  | None (stable condition and improved angina) |

Abbreviations: EnD-CAD: end-stage diffuse coronary artery disease; ESRD: end-stage renal disease; No.: number; Age (years); ESWT: extracorporeal shock wave therapy; W: Waiting list; M: male, F: female, mo: month(s); HFpEF: heart failure with preserved ejection fraction; NSTE-ACS: non-ST segment elevation acute coronary syndrome; s/p: status post; PVD: peripheral vascular disease; PTA: percutaneous transluminal angioplasty.
We noted the prevalence of cancer and incidences of sepsis and heart failure were higher in the EnD-CAD/ESRD group than those in the EnD-CAD group. Also, even with significantly lower lipid profile which might falsely bias favored outcomes, the incidence of unfavorable clinical outcomes remained substantially high in the ESRD subpopulation. The findings from the current study were consistent with previous reports [26,27] showing the major leading causes of death in ESRD are cardiovascular disease, infection, and malignancy. Besides, ESRD patients are vulnerable to immune dysfunction, systemic infection, fluid overload, and imbalance of acid-base or electrolyte [26,27]. These observations were additionally explained why we terminated the study after finding no benefit of ESWT on LV function improvement and circulating EPC expression even though there was insufficient case enrollment. Longer-term follow-up for the safety and efficacy of ESWT in both high-risk groups needs further investigation.

This study has limitations. First, the sample size was relatively small, and therefore statistical significance of some variables or outcomes could be distorted. Second, shame control group (i.e., receiving standard medical therapy alone) was not set up because the case number of EnD-CAD/ESRD patients was too limited for further allocation, i.e., only 8 cases were identified to receive ESWT during 3-year study period. In light of slow and hard process in case screening and enrollment, we encourage to conduct a multi-center double-blinded randomization study for the EnD-CAD/ESRD patients to investigate whether cardiac ESWT is really ineffective in such kind of high-risk population. Third, the cellular activity and number of circulating EPCs as well as angiogenic or inflammatory biomarkers such as VEGF, hepatocyte growth factor, fibroblast growth factor or stromal cell-derived factor 1 were not checked in the present study owing to limited research budget and study period, so the mechanism why the effects of SW therapy were unstable in the ESRD population was not clarified in detail. Finally, high rate of adverse events and unfavorable outcomes as well as lack of effectiveness on the LVEF improvement and cardiac remodeling blocked further conduction of this clinical research.

Conclusions

The patients with EnD-CAD and ESRD were at high risk for development of adverse clinical events and had high rate for morbidity and mortality. Cardiac ESWT seemed effective on the symptomatic relief for angina and dyspnea, whereas it did not improve angiogenesis, LV systolic function, and cardiac remodeling. Application of cardiac ESWT as a therapeutic modality in EnD-CAD/ESRD should be deeply thought over.

Availability of data and materials

The datasets generated and analyzed are not publicly available due to patient privacy considerations, but are available from the corresponding author on reasonable request.

Conflicts of interest

All authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2020.10.004.

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