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Shock Waves
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ORIGINAL ARTICLE

Extracorporeal cardiac shock wave therapy for ischemic heart disease

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Abstract Prognosis of severe ischemic heart disease with no indication of percutaneous coronary intervention or coronary artery bypass grafting still remains poor. Extracorporeal shock wave therapy was introduced for medical therapy more than 20 years ago to break up kidney stones. We have demonstrated that extracorporeal cardiac shock wave therapy at a low level of ~10% of energy density that used for urinary lithotripsy treatment, effectively induces coronary angiogenesis and improves myocardial ischemia in a porcine model of chronic myocardial ischemia in vivo. On the basis of the promising results in animal studies, we have recently developed a new, non-invasive angiogenic therapy with low-energy shock waves for ischemic heart disease. Our extracorporeal cardiac shock wave therapy improved symptoms and myocardial ischemia in patients with severe coronary artery disease. These beneficial effects of the shock wave therapy persisted for at least 12 months. Importantly, no procedural complications or adverse effects were noted. These results indicate that our extracorporeal cardiac shock wave therapy is an effective and non-invasive treatment for ischemic heart disease. To further confirm the usefulness and safety of our SW therapy, we are currently conducting the second clinical trial in a randomized and placebo-controlled manner.

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1 Introduction

Ischemic heart disease is the leading cause of death in developed countries and the number of patients is increasing worldwide [1]. Since the coronary arteries supply blood to the heart muscle, narrowing or closure of the arteries by atheromatous plaques limits blood flow to a part of heart muscle, causing an imbalance between oxygen supply and demand with a resultant development of myocardial ischemia. Myocardial ischemia can cause temporary chest pain (angina pectoris), permanent heart muscle damage (acute myocardial infarction), lethal arrhythmia, and sudden cardiac death. The current management of ischemic heart disease has three major therapeutic options, including medical treatment (drug therapy), percutaneous coronary intervention (PCI; balloon dilation of narrowed arteries), and coronary artery bypass grafting (CABG; heart surgery). However, prognosis of patients with severe coronary artery disease without indication of PCI or CABG still remains poor because medication is the only therapy to treat the disorder. Thus, it is crucial to develop an alternative therapy for severe ischemic heart disease. Currently, gene therapy and cell-based therapy for those patients are under development, however, most of these therapies are invasive in nature and their effectiveness and safety have not been established yet [2–4]. We have recently developed a new, non-invasive angiogenic therapy using low-energy shock waves (SW) [5–7]. In this article, we outline our recent works in animals and humans, and then discuss the

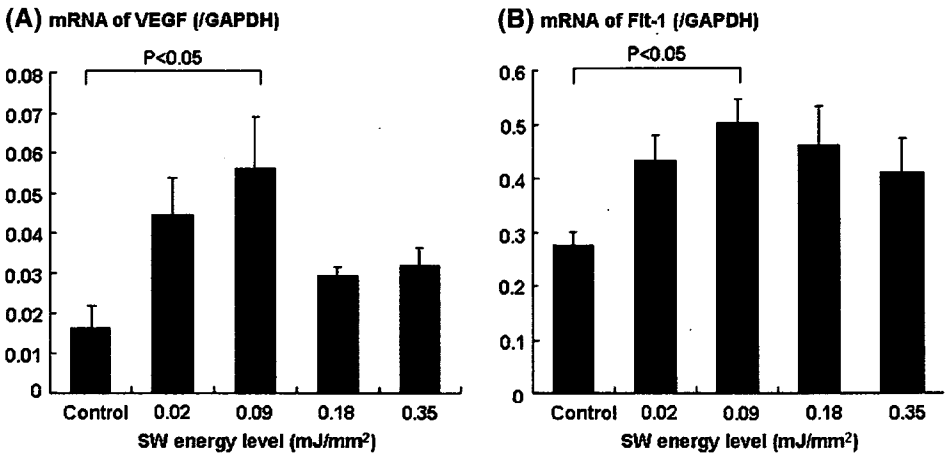

Fig. 1 SW treatment up-regulates mRNA expression of VEGF **a** and Flt-1 **b** in HUVECs in vitro with a maximum effect noted at 0.09 mJ/mm^2. Results are expressed as mean ± SEM (n = 10 each) (quoted from Ref. [5] with permission)

mechanisms for SW-induced angiogenesis and advantages of our cardiac SW therapy.

2 Extracorporeal cardiac SW therapy for angina pectoris

2.1 In vitro study

Extracorporeal SW therapy has been introduced for medical therapy more than 20 years ago to break up kidney stones, which has markedly improved the treatment of urolithiasis. Furthermore, the lithotripsy therapy with SW is indicated for gallstones, pancreatic and salivary stones, and is also used for the treatment of certain orthopedic conditions, such as bone fracture and calcifying tendonitis [8,9].

It was demonstrated that a low level of SW could up-regulate angiogenic factors in vitro [10] and induce localized stress on cell membranes that resembles shear stress [11]. We have recently reported that a low level of SW enhances the expression of vascular endothelial growth factor (VEGF) and its receptor, Flt-1, in cultured human endothelial cells (HUVEC) in vitro with a maximum effect noted at 0.09 mJ/mm^2, which level is approximately 10% of that used for urinary lithotripsy treatment (Fig. 1) [5].

2.2 Animal studies

In the clinical setting, the goal for the treatment of ischemic heart disease should include not only enhancement of angiogenesis but also recovery of ischemia-induced myocardial dysfunction. We performed in vivo animal experiments with pigs, in which myocardial ischemia was made by placing an ameroid constrictor at the proximal segment of the left circumflex coronary artery (LCX) that gradually induced a total occlusion of the artery with sustained myocardial dysfunction but without myocardial infarction in 4 weeks [5]. Thereafter, we performed extracorporeal SW therapy to the ischemic myocardial region (n = 8). On the basis of our in vitro experiment, we applied a low energy of SW (0.09 mJ/mm^2) to nine spots in the ischemic LCX region (200 shots/spot) with a guidance of an echocardiogram equipped within a specially designed SW generator (Storz Medical AG, Tägerwilen, Switzerland). We were able to focus SW on any part of the heart under the guidance of echocardiography. In order to treat the targeted ischemic myocardium without inducing ventricular arrhythmia, we applied SW at end-diastole during cardiac cycle with a R-wave-triggered system. We performed the SW treatment (n = 8) at 4 weeks after the implantation of an ameroid constrictor 3 times within 1 week, whereas animals in the control group (n = 8) received the same anesthesia procedures 3 times a week but without the SW treatment. We evaluated cardiac function at ameroid implantation (baseline) and at 4 and 8 weeks after the implantation.

Four weeks after the implantation of an ameroid constrictor, wall motion of the LCX (posterolateral) region in the left ventricle (LV) was equally reduced in both the control and the SW group before the SW therapy (Fig. 2a, c). However, 4 weeks after the SW therapy, left ventriculography showed marked improvement of LV wall motion only in the SW (Fig. 2b, d). The SW therapy normalized LV ejection fraction in the SW group but not in the control group (Fig. 2e). In this study, the SW treatment normalized global and regional myocardial functions as well as regional myocardial blood flow in the chronic ischemic region evaluated with colored microspheres. In addition, the SW treatment increased vascular density in the SW-treated region and up-regulated VEGF expression in the ischemic myocardium in vivo (Fig. 3). Importantly, no procedural complications or adverse effects were noted during or after the SW treatment. These data indicate that the SW treatment up-regulated the endogenous angiogenic system in pigs in vivo, suggesting its usefulness for the treatment of ischemic heart disease in humans.

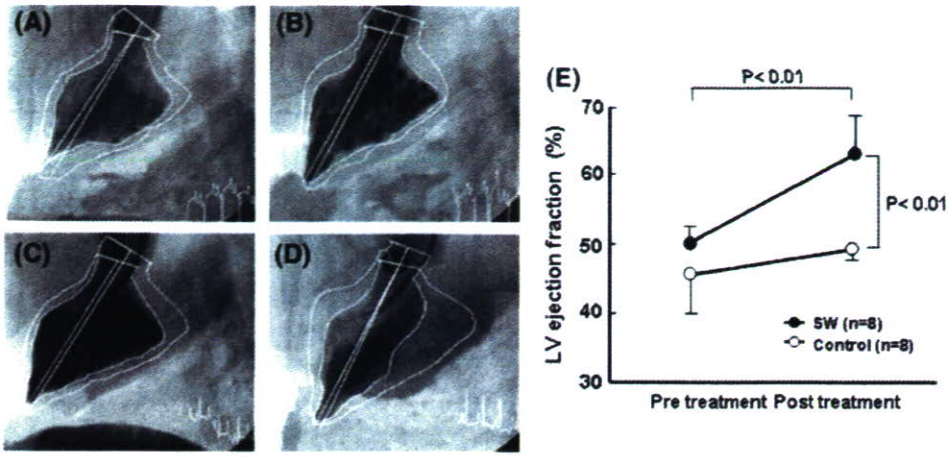

Fig. 2 Extracorporeal cardiac SW therapy improves ischemia-induced myocardial dysfunction in vivo as evaluated with left ventriculography. Four weeks after the implantation of an ameroid constrictor, LV wall motion of the LCX (posterolateral) region was reduced in both the control **a** and the SW group (before the SW therapy) **c**. Eight weeks after the implantation of an ameroid constrictor, no significant change in LV wall motion was noted in the control group **b**, whereas marked recovery was noted in the SW group **d**. **e** The SW therapy normalized LV ejection fraction in the SW group but not in the control group. Results are expressed as mean ± SEM ($n = 8$ each) (quoted from Ref. [5] with permission)

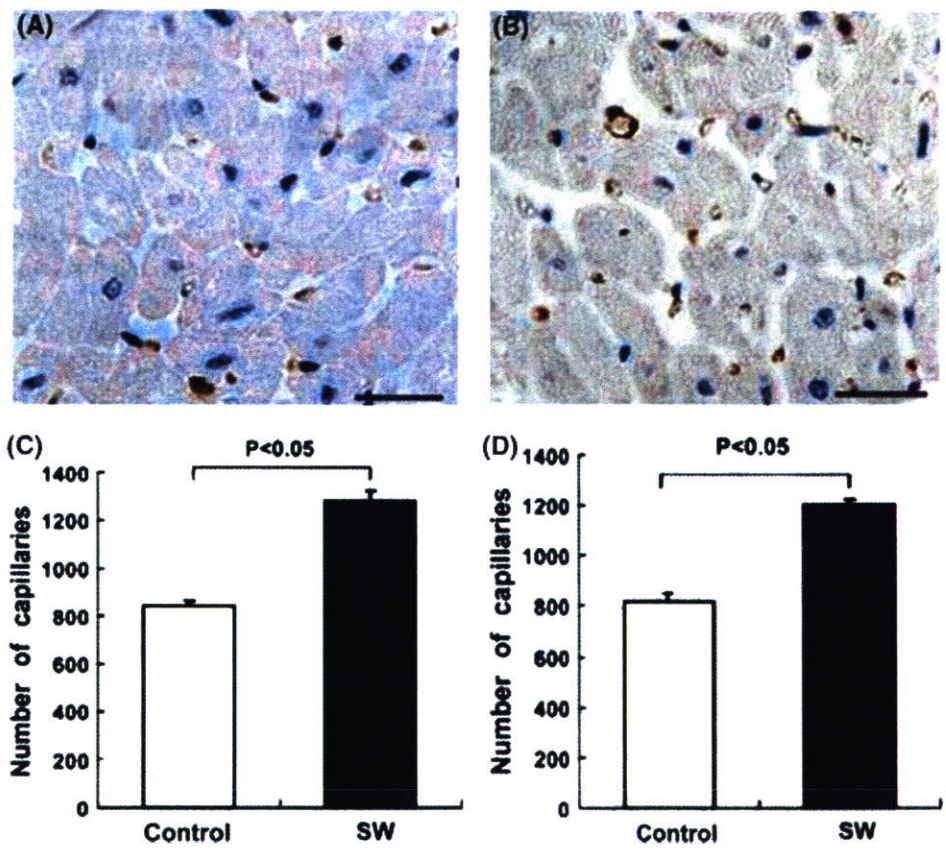

Fig. 3 Extracorporeal cardiac SW therapy increases the density of factor VIII-positive capillaries in the ischemic myocardium. Factor VIII staining of the LCX region from the control **a** and the SW group **b**. *Scale bar* represents 20 μm. Capillary density was significantly greater in the SW group (SW) than in the control group (Control) in both the endocardium **c** and the epicardium **d**. Results are expressed as mean ± SEM ($n = 6$ each) (quoted from Ref. [5] with permission)

2.3 Clinical studies

On the basis of the promising results in animal studies, we started the first clinical trial of cardiac SW therapy in humans in 2003. We treated nine patients with end-stage ischemic heart disease with no indication of PCI or CABG (55–82 years old, five men and four women) with our cardiac SW therapy (200 shots/spot at 0.09 mJ/mm^2 for 20–40 spots, 3 times a week/series) (Fig. 4) [6]. As shown in Fig. 4a, patients just lied down on the bed without anesthesia during

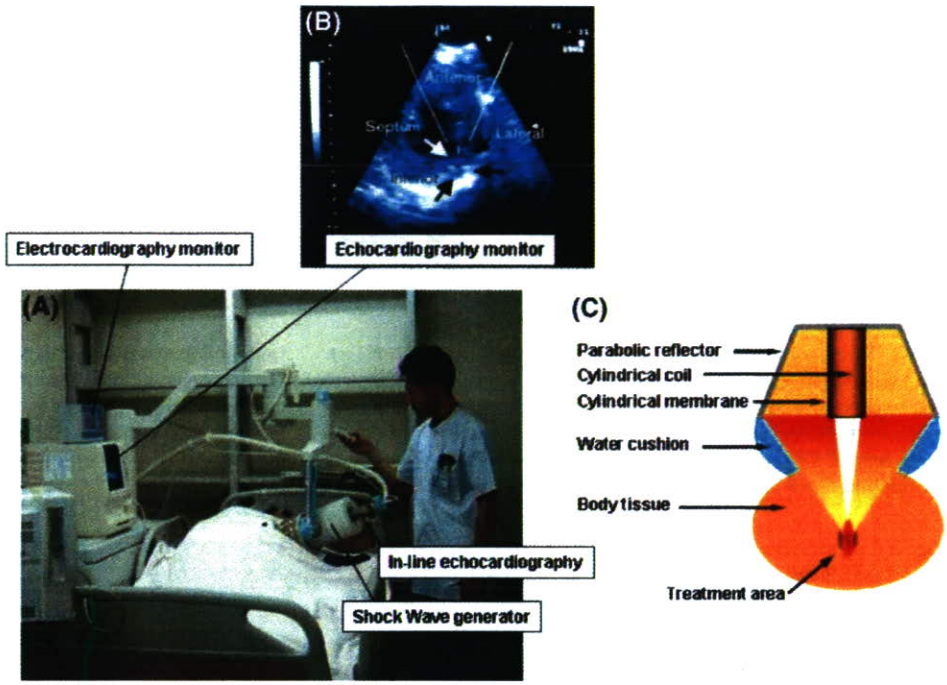

Fig. 4 Extracorporeal cardiac SW therapy in action in a patient with severe coronary artery disease. **a** The machine is equipped with a SW generator and in-line echocardiography. The SW generator is attached to the chest wall when used. **b** The cardiac ultrasound monitor. The SW pulse is easily focused on the ischemic myocardium under the guidance of echocardiography (*black* and *white arrows*). **c** The SW generator is equipped with parabolic reflector, cylindrical coil, and cylindrical membrane with water cushion

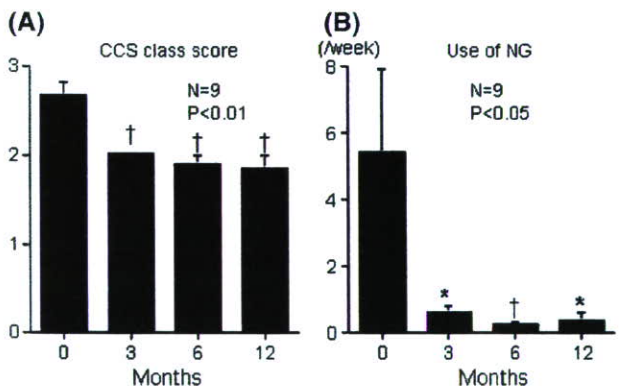

Fig. 5 Extracorporeal cardiac SW therapy significantly improved Canadian Cardiovascular Society (CCS) scores **a** and the use of nitroglycerin (NG) **b**. Results are expressed as mean ± SEM. $*P < 0.05$ and $\dagger P < 0.01$ vs. 0 month (statistically analyzed by post-hoc test after one-way ANOVA) (quoted from Ref. [6] with permission)

the treatment. The SW therapy improved symptoms and reduced nitroglycerin use (Fig. 5) as well as myocardial perfusion as assessed by dipyridamole stress thallium scintigraphy only in the ischemic area treated with the therapy (Fig. 6). These beneficial effects of the SW therapy persisted for at least 12 months (Figs. 5 and 7). No procedural complications or adverse effects were noted. These data indicate that our extracorporeal cardiac SW therapy is an effective and non-invasive treatment for end-stage ischemic heart disease. To further confirm the usefulness and safety of our SW therapy, we are currently conducting the second clinical trial in a randomized and placebo-controlled manner.

3 Extracorporeal cardiac SW therapy for acute myocardial infarction

Acute myocardial infarction (AMI) is associated with a loss of heart muscle. After AMI, the heart is gradually dilated and cardiac ability to pump blood to the rest of the body is impaired. This process is called "LV remodeling" [1]. The development of LV remodeling leads to sudden cardiac death, heart failure, and poor prognosis. If sufficient angiogenesis can be induced in the border zone of infarcted myocardium, the progression of LV remodeling could be suppressed with a resultant improvement of prognosis. Therefore, we examined whether our SW therapy is also effective to ameliorate LV remodeling after acute myocardial infarction in pigs.

Acute myocardial infarction was created by surgically excising the proximal segment of the LCX [7]. In the early treatment protocol, the SW therapy was started 3 days after AMI, whereas in the late treatment protocol, the SW therapy was started 4 weeks after AMI ($n = 5$ each). The remaining animals were treated in the same manner but without the SW treatment in each protocol ($n = 5$ each). In the early treatment protocol in which the treatment was started at 3 days after AMI, LV ejection fraction and LV end-diastolic volume were significantly improved in the SW group compared with the control group at 4 weeks after the treatment (Fig. 8). Furthermore, regional myocardial blood flow and number of capillaries in the border zone were significantly improved in the SW group compared with the control group. By contrast, in the late treatment group in which the SW treatment was started 4 weeks after AMI, no such beneficial

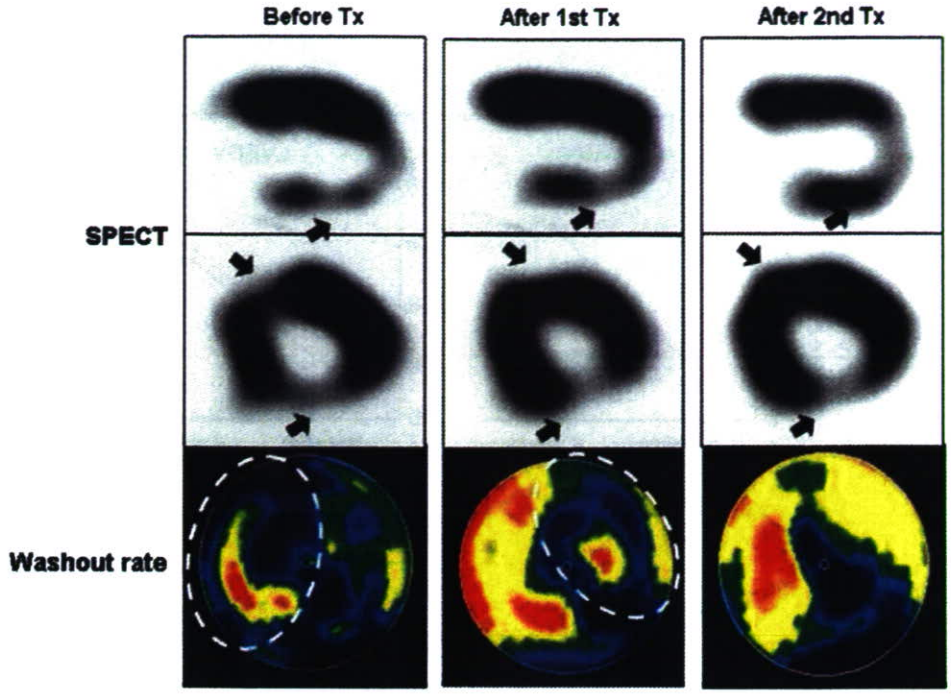

Fig. 6 Dipyridamole stress thallium-201 single photon emission computed tomography (SPECT) imaging and polar map demonstrated that the SW treatment ameliorated myocardial perfusion only where SW was applied; in the anteroseptal wall after the first treatment (Tx) and in the lateral wall after the second treatment (*arrows*). The areas where shock waves were shot were indicated with *dotted lines*. (quoted from Ref. [6] with permission)

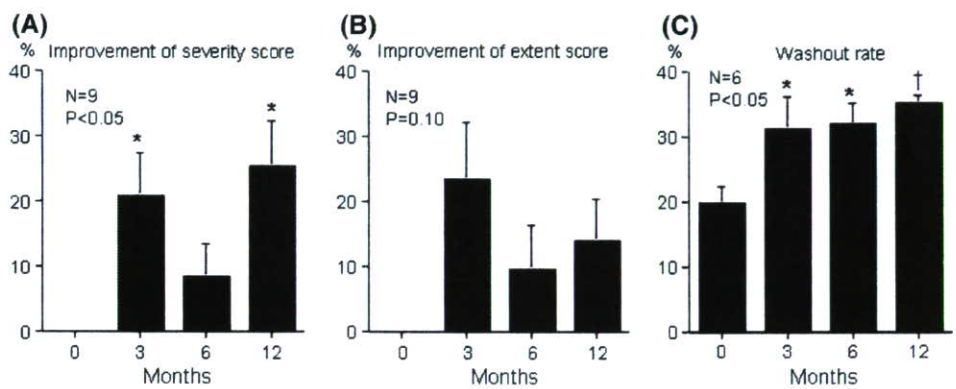

Fig. 7 The SW therapy significantly improved severity score **a**, tended to improve extent score **b**, and significantly improved local washout rate in patients with initial low washout rate (<30%) **c** in the dipyridamole stress thallium scintigraphy. Results are expressed as mean ± SEM. $*P < 0.05$ and $\dagger P < 0.01$ vs. 0 month (statistically analyzed by post-hoc test after one-way ANOVA) (quoted from Ref. [6] with permission)

effects of the SW therapy were noted. These results suggest that our extracorporeal cardiac SW therapy is an effective and non-invasive therapy to ameliorate LV remodeling after AMI when started in the early phase of the disorder. We are currently conducting the first clinical trial in patients with AMI who are successfully treated with PCI, in order to examine whether our SW therapy combined with PCI ameliorates LV remodeling and dysfunction after AMI in humans.

4 Mechanisms for SW-induced angiogenesis

When a SW hits tissue, cavitation (a micrometer-sized violent collapse of bubbles) is induced by the first compression by the positive pressure part and the expansion with the tensile part of a SW [12]. Because the physical forces generated by cavitation are highly localized, SW could induce localized stress on cell membranes, as altered shear stress affects endothelial cells [13]. Recent reports have demonstrated the biochemical effects of SW, including hyperpolarization and Ras activation [14], non-enzymatic nitric oxide synthesis [15], and induction of stress fibers and intercellular gaps [16].

Enhanced expression of multiple angiogenic factors, such as VEGF and stromal-derived factor 1 (SDF-1), is crucial for the recruitment and incorporation of endothelial progenitor cells (EPCs) [17–22]. VEGF is known to induce angiogenesis by activating mobilization and homing of EPCs from the bone marrow to ischemic tissue [17–20]. We have previously demonstrated that our SW therapy up-regulates the expression of both VEGF and its receptor Flt-1 in cultured human endothelial cells and increases capillary density and regional myocardial blood flow in a porcine model of myocardial

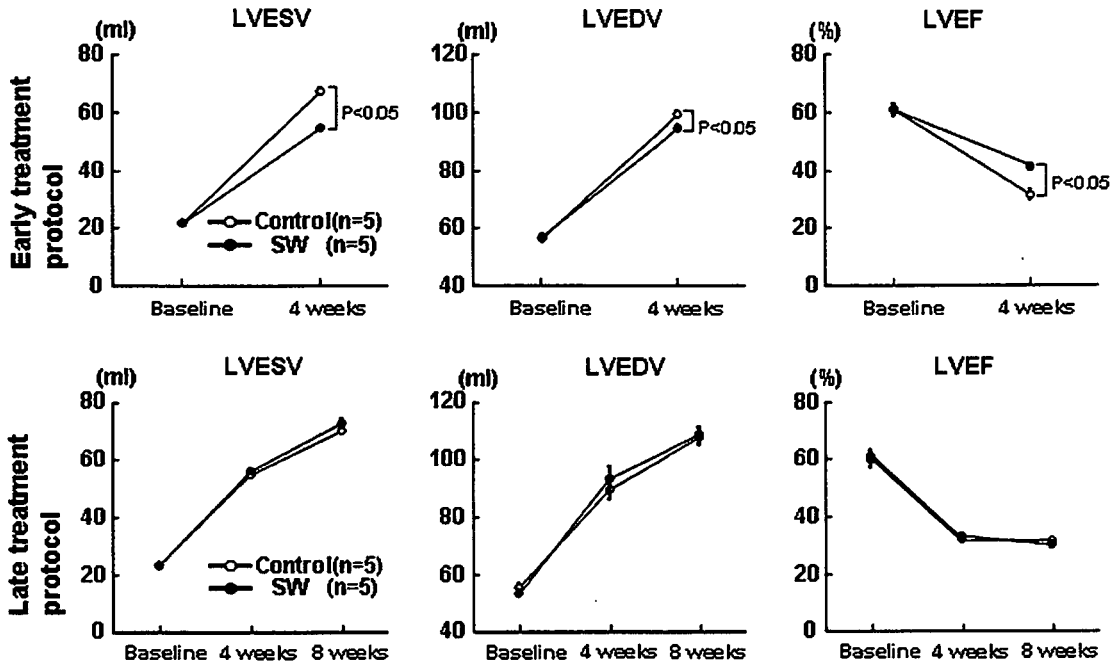

Fig. 8 Results of left ventriculography for the inhibitory effects of the cardiac SW therapy on the development of LV remodeling after AMI. The inhibitory effects of the SW therapy were noted in the early treatment protocol (*upper panel*) but not in the late treatment protocol (lower panel). *LVESV* left ventricular end-systolic volume, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction. Results are expressed as mean ± SEM ($n = 5$ each) (quoted from Ref. [7] with permission)

ischemia [5]. Recently, it was reported that SDF-1 is essential for the retention of pro-angiogenic stem cells in peripheral organs, although the up-regulation of VEGF is sufficient to mobilize stem or progenitor cells from the bone marrow to the systemic circulation [21,22]. Therefore, it is possible that our SW therapy enhances the incorporation of circulating EPCs by up-regulating the expression of SDF-1 in ischemic myocardium. This notion has been supported by the recent study by Aicher et al. [23] that combination of SW therapy enhances the efficacy of the cell-based angiogenic therapy. Further studies are needed to elucidate the precise molecular mechanisms involved in the beneficial effects of SW in the treatment of ischemic heart disease.

5 Advantages of extracorporeal cardiac SW therapy

Recent attempts to enhance angiogenesis in ischemic organs include gene therapy and bone marrow cell transplantation therapy. However, the need of invasive procedure to deliver those cells to the ischemic myocardium severely limits the usefulness of those therapies in clinical situations. A major advantage of our extracorporeal cardiac SW therapy over those strategies is shown by the fact that it is quite non-invasive and safe without any adverse effects. If necessary, we are able to repeatedly treat patients (even outpatients) with our SW therapy because 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 severe coronary artery disease. Indeed, the SW treatment itself already has been clinically established as an effective and safe treatment for lithotripsy and chronic plantar fasciitis [24,25]. Thus, our extracorporeal cardiac SW therapy appears to be an applicable and non-invasive treatment for ischemic heart disease in humans.

6 Conclusions

We have successfully developed an extracorporeal cardiac SW therapy with a low energy SW, which may be an effective, safe, and non-invasive therapy for the treatment of severe ischemic heart disease in humans. Also, the cardiac SW therapy had no procedural complications or adverse effects.

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循環器科，61(4)：372-377，2007

話　題

体外衝撃波治療*

伊藤健太**　下川宏明**

Key Words：shock wave therapy, angiogenesis, ischemic heart disease, angina pectoris, myocardial infarction

はじめに

虚血性心疾患に対する治療は生活習慣の改善をベースに，①薬物療法，②カテーテルを用いた冠動脈インターベンション(percutaneous coronary intervention：PCI)，③冠動脈バイパス手術(coronary arterial bypass grafting：CABG)の3本柱から成る．近年わが国では，人口の高齢化や生活習慣の欧米化・糖尿病患者の増加に伴い，PCIやCABGを施行できないようなびまん性狭窄病変をもつ症例など，従来の治療法では十分な治療効果を得られない重症の虚血性心疾患症例が増加してきている．このような症例では，胸痛のため生活の質(QOL)が低下するのみならず，慢性心筋虚血による心機能低下のため，重症の心不全へと進行し予後も不良である．そのため，新たな治療法の開発が望まれている．

近年，閉塞性動脈硬化症や虚血性心疾患に対して遺伝子治療や未分化細胞移植治療が試みられ，日本を含めた世界各国で臨床試験が行われている．これらの治療では，未分化細胞の採取や遺伝子・細胞の送達のために全身麻酔下での骨髄穿刺や開胸操作といった大きな侵襲を伴う．そのため患者への身体的負担は大きく，また繰り返し行うことは困難である．さらに，有効性・安全性が認められたとしても，費用が高額にな

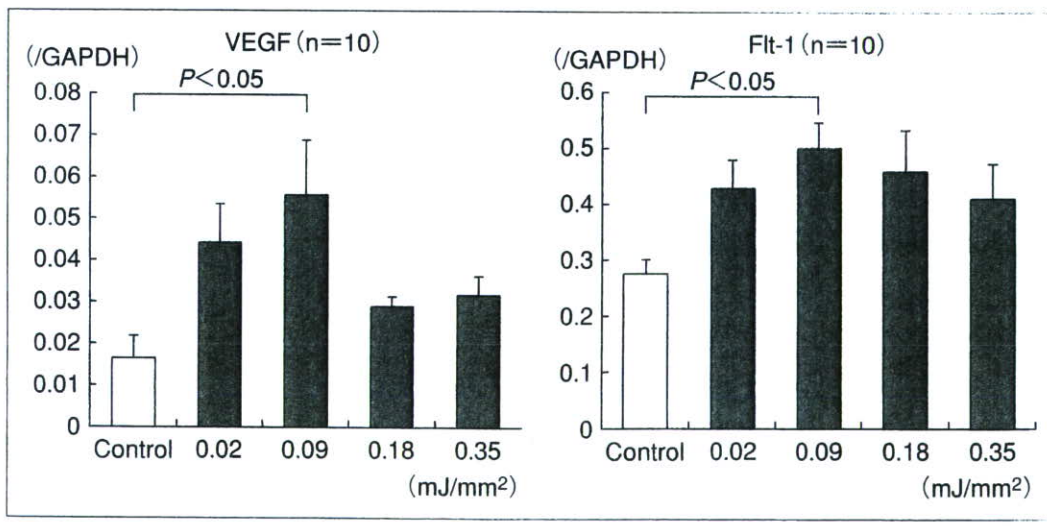

図1　衝撃波によるヒト培養内皮細胞(HUVEC)における血管新生因子の発現亢進
(文献[6]より改変)

* Extracorporeal cardiac shock wave therapy.

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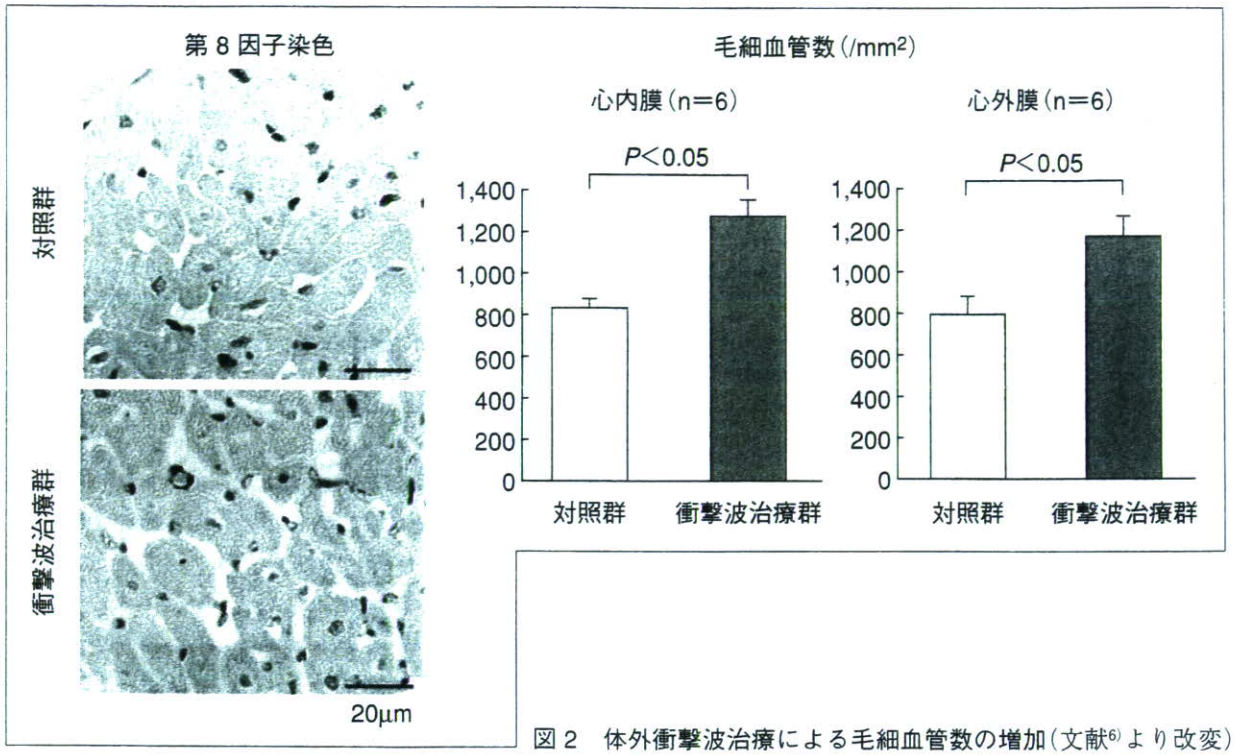

図2　体外衝撃波治療による毛細血管数の増加(文献[6]より改変)

る．一方，最近では，遺伝子治療や細胞移植治療について，動物実験の結果から期待されたほどの有効性が臨床試験において認められていないことも指摘されている[1)~5)]．そのため，低侵襲で有効性の期待できる治療法の開発が期待されている．

われわれは虚血性心疾患患者を対象に，低出力の衝撃波を用いた血管新生療法を開発し，現在，重症狭心症患者に対する臨床試験と急性心筋梗塞患者に対する臨床試験を行っている．

低出力の衝撃波による血管新生作用

衝撃波とは音速を超えて伝わる圧力波で，同じような音響的特性をもつ媒体内を伝播していくことから，体外で発生させた衝撃波を皮膚表面から脂肪・筋肉などの体組織を通って伝播させ，体内深部の一点に収束させることができる．衝撃波を用いた治療法としては，尿路結石などの結石破砕治療が確立している．われわれは基礎実験により，ヒト臍帯静脈内皮細胞(human umbilical vein endothelial cells：HUVEC)に衝撃波を照射すると，結石破砕に用いる出力の約10％という弱い出力(0.09mJ/mm²)をピークに，主要な血管新生因子である血管内皮増殖因子(vascular endothelial growth factor：VEGF)およびその受容体であるFlt-1の発現が増加することを確認した(図1)[6)]．そこで，ブタ慢性心筋虚血モデルを作成して体外衝撃波治療の効果を検討した．慢性虚血心筋に1か所あたり200発の衝撃波を9か所照射し，4週間後に評価を行った．その結果，体外衝撃波治療により，虚血心筋におけるVEGFの発現が遺伝子レベル・蛋白レベルのいずれでも亢進していた．さらに，毛細血管数の増加(図2)と冠血流の有意な増加，それに伴う左室壁運動の改善を認めた[6)]．衝撃波治療中および治療後のホルター心電図では重篤な不整脈を認めず，突然死も認めなかった．組織学的検討においても，出血などの組織損傷は認められなかった．以上の結果から，低出力の衝撃波を用いた体外衝撃波治療は，安全で有効な血管新生療法であることが確認された．

重症狭心症に対する体外衝撃波治療

上記の基礎的検討に基づき，われわれは，重症狭心症に対して体外衝撃波治療の臨床試験を行っている．対象は，①20歳以上，②最大量の薬物治療に抵抗性で，かつPCIやCABGで完全な血行再建が不可能，③カナダ心臓病学課分類(CCS)

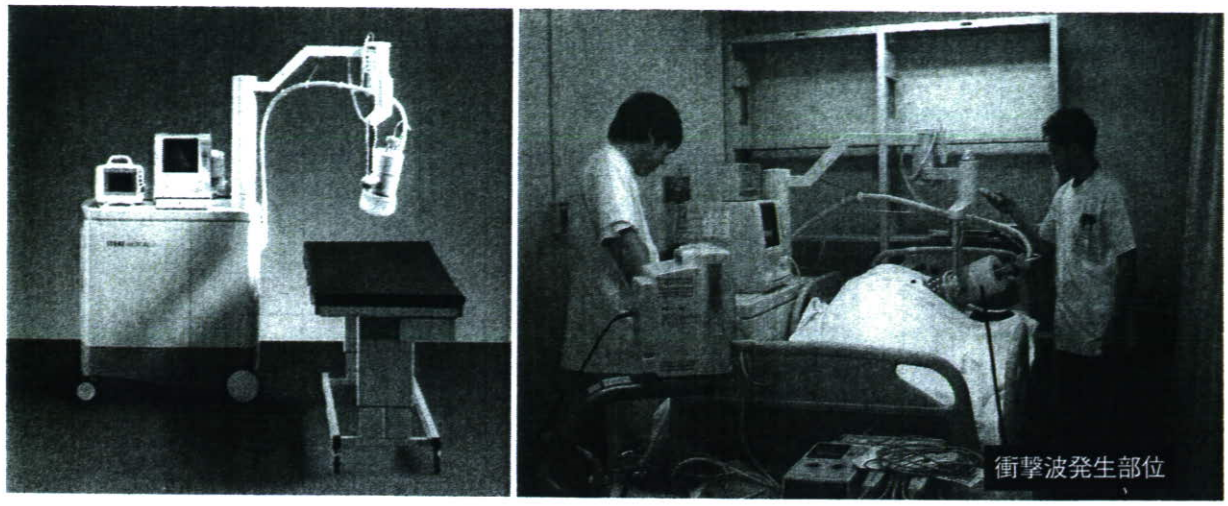

図3　非侵襲性体外衝撃波治療装置(左)と治療風景(右)

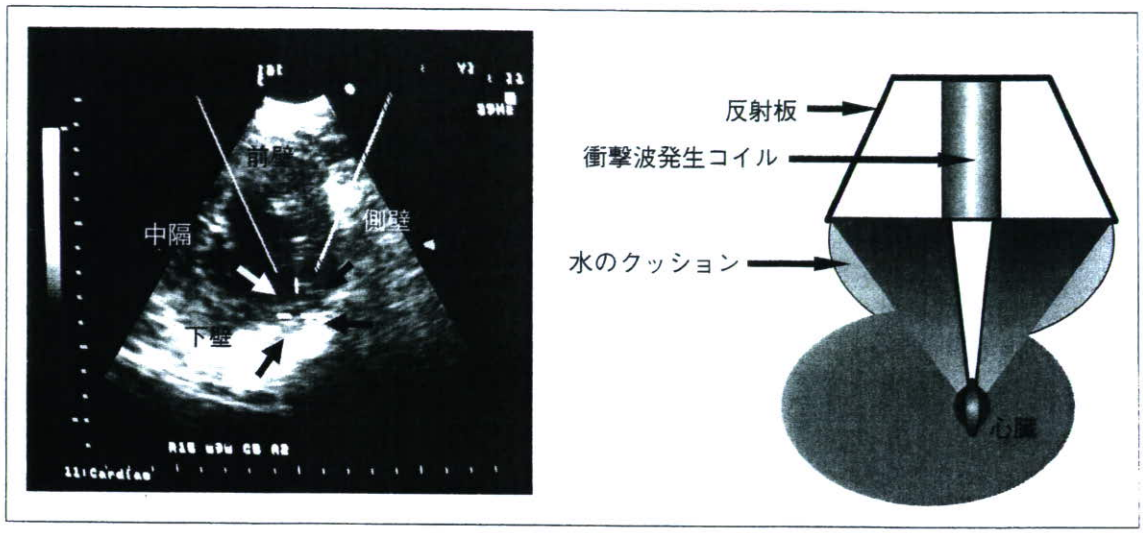

図4　衝撃波治療の方法
心臓超音波検査画面(左)と概念図(右)．(文献[7]より改変)

でClass II～IV,④負荷心筋シンチや負荷心エコーで明らかな虚血領域を認める重症狭心症とした．実際の治療には，スイスのメーカーと共同開発した心臓病治療専用の衝撃波治療装置を用いる(図3)．装置に内蔵した超音波プローブを患者の前胸壁にあてて，心臓を観察しながら虚血部位に照準を合わせ，衝撃波を照射する．1か所につき200発の衝撃波を，虚血領域の広さに応じて20～120か所照射する(図4)．1回の治療時間は約3時間で，1日おきに3回治療を行う．痛みや苦痛を伴わないため，麻酔や鎮静薬の投与は必要ない．ただし，衝撃波は空気があると破裂する性質があるため，慎重に肺を避ける必要がある．2003年1月から重症狭心症患者9名を対象に九州大学で実施した第一次臨床試験では，個人差はあるものの全例で胸痛の自覚症状が軽減し，またニトログリセリンの使用量が激減するなどの効果を認め，その効果は1年以上にわたって持続している(図5)[7]．自覚症状のみならず，負荷心筋シンチグラムで評価した心筋灌流も，低出力の衝撃波を照射した部位において改善を認めた[7]．図6にあげた例では，1回目の治療で左室前壁中隔に対して体外衝撃波治療を行ったところ，治療部位においてのみ心筋灌流が改善した．さらに2回目の治療で左室側壁に対して体外衝撃波治療を行ったところ，今度は側壁領域の心筋灌流が改善した．この結果から，衝撃波治療を照射した部位のみで血管新生が生じ，心筋灌流が改善したと考えられた．一方，治療に伴う合併症や副作用はまったく認めなかった．

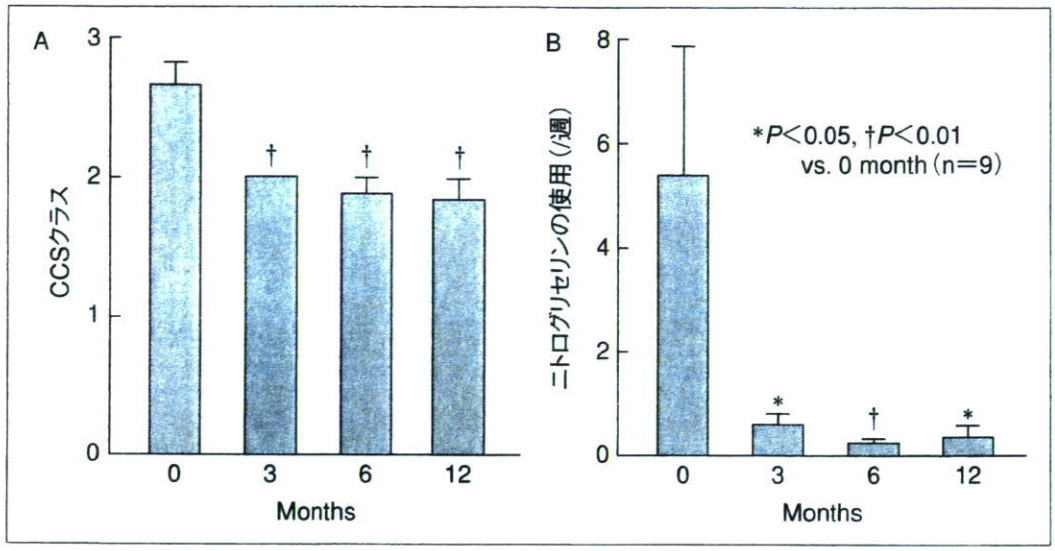

図5　体外衝撃波治療による自覚症状の改善（文献[7]より改変）

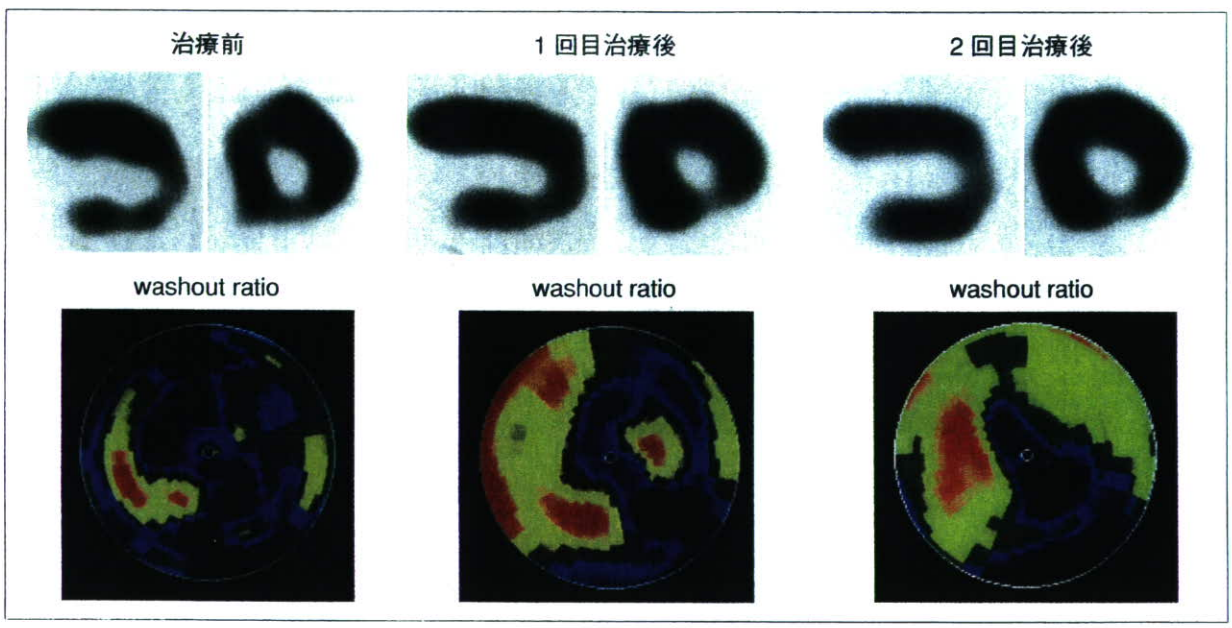

図6　体外衝撃波治療による心筋灌流の改善（文献[7]より改変）

有効性をさらに科学的に評価するために，2005年11月から東北大学病院において，衝撃波治療とプラセボ治療を比較する第二次臨床試験が進行中である．3か月間隔で衝撃波治療とプラセボ治療を一度ずつ受けるプロトコールとなっており，初回に衝撃波治療を受けた症例は3か月後にプラセボ治療を受け，初回プラセボ治療を受けた症例は3か月後に衝撃波治療を受けることになる．

急性心筋梗塞に対する体外衝撃波治療

わが国では，急性心筋梗塞の発症早期にPCIによる再灌流療法が行われ，心筋梗塞発症早期の死亡率低下に貢献している．しかし，慢性期には十分な薬物治療を受けていても左室リモデリング（心拡大と収縮能低下）が進行し，重篤な心不全へ進行する例が少なくない．再灌流療法成功後も，梗塞巣周囲では組織の浮腫などにより微小血管の血流が完全には改善せず心筋は虚血にさらされており，これが左室リモデリング進行の一因と考えられている．そこでわれわれは，ブタ急性心筋梗塞モデルを用いて，体外衝撃波治療が慢性期の左室リモデリングを抑制するか検討した．急性心筋梗塞作成3, 6, 9日目に体外

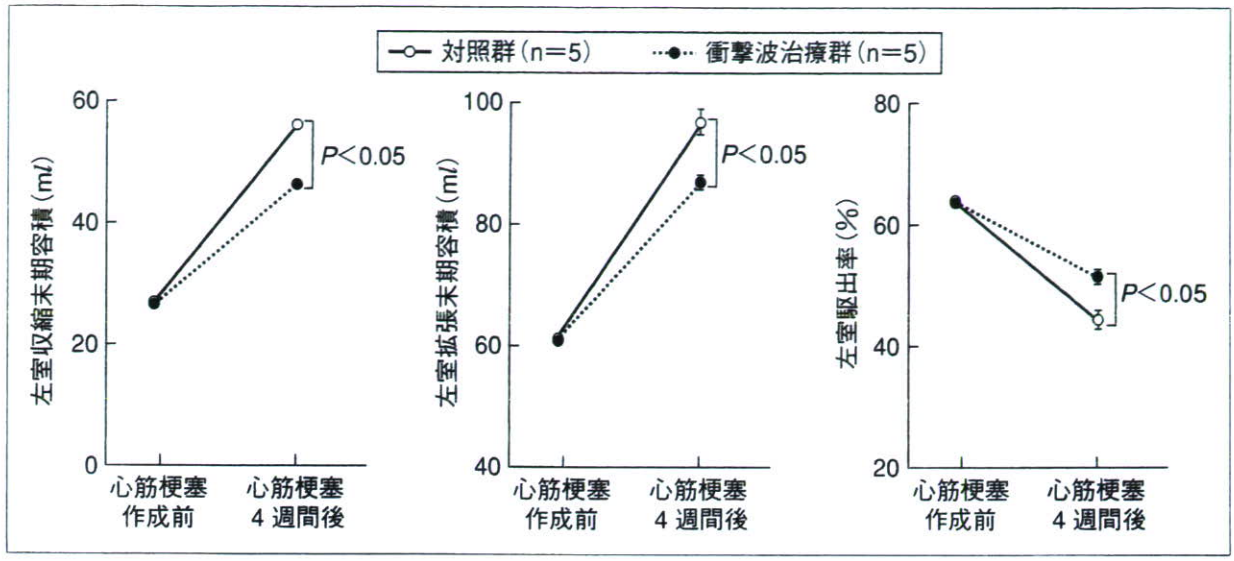

図7　体外衝撃波治療による左室リモデリングの抑制(文献[8]より改変)

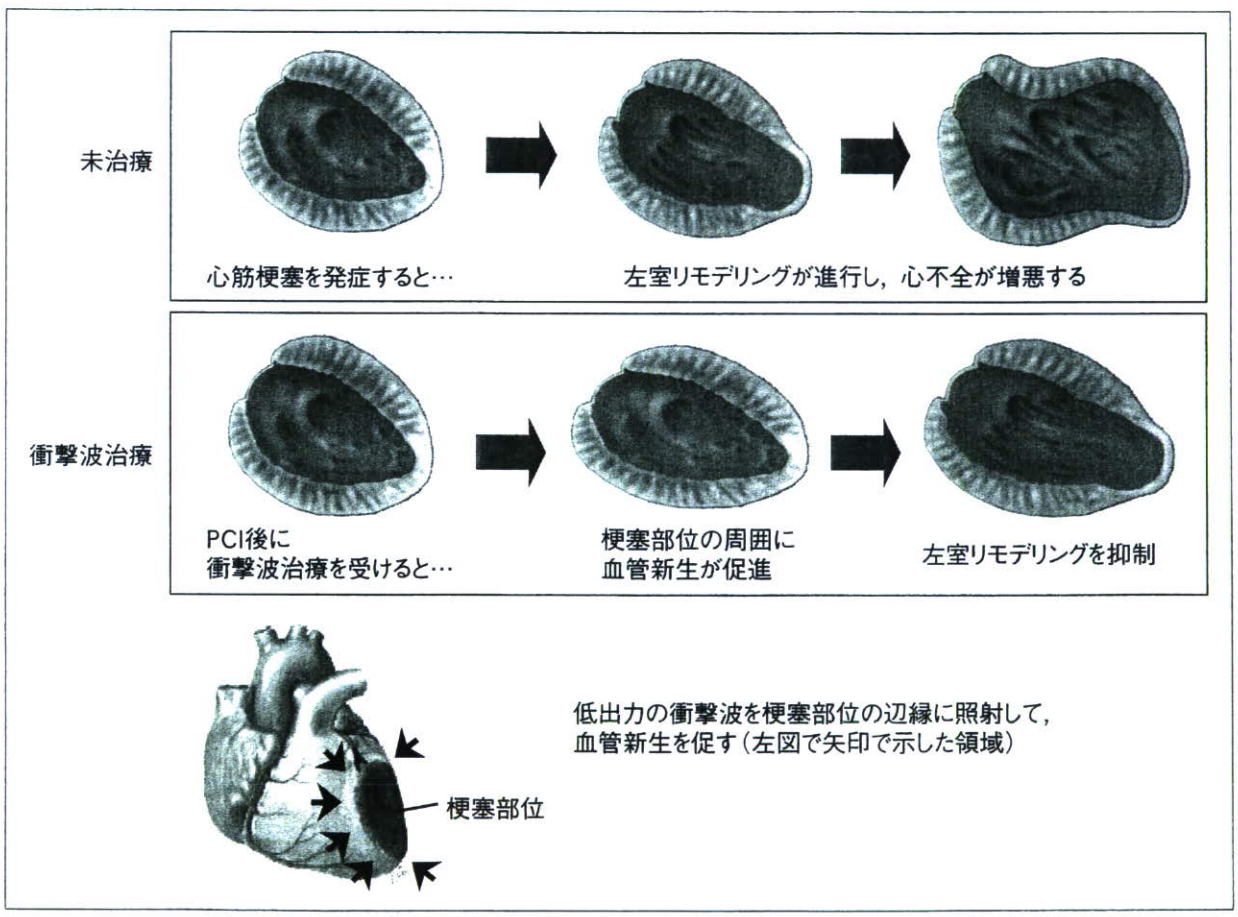

図8　急性心筋梗塞に対する体外衝撃波治療の効果

衝撃波治療を行い，4週間後に評価を行ったところ，体外衝撃波治療により慢性期の左室容積の拡大が抑制され収縮能の低下が軽減された．つまり，左室リモデリングが抑制されることが確認された(図7)[8]．梗塞巣周囲の毛細血管数が増加していたことから，急性期の体外衝撃波治療により境界領域での血管新生が促進されることにより梗塞サイズの拡大が抑制されたことが，左室リモデリング抑制のメカニズムの一つと考えられた(図8)．東北大学病院では東北大学医

学部倫理委員会の承認を得て，2007年2月から急性心筋梗塞に対する体外衝撃波治療の臨床試験が進行中である．この試験では，PCIによる再灌流療法が成功した症例に対して，心筋梗塞発症72時間以内に衝撃波治療を開始し，1～2日おきに計3回行う．1年間追跡し，安全性と慢性期の左室リモデリング抑制効果・心不全発症抑制効果を評価する．

おわりに

われわれが開発している重症虚血性心疾患に対する体外衝撃波治療は，きわめて低侵襲であり，血管新生を促進することにより心筋灌流を改善することが期待される新しい治療法である．今後，その安全性・有効性がさらに確認できれば，外来での治療も可能になると考えられる．さらに，すでにウサギを用いた検討で閉塞性動脈硬化症に対する有効性・安全性は確認しており，閉塞性動脈硬化症や脳梗塞などの動脈硬化性疾患への応用も期待できる．近年，整形外科領域でも肘や肩，足底などの疼痛治療や難治性の骨折の治療にも低出力の衝撃波が試みられており，今後，幅広い疾患への応用が期待されている治療法である[9)10)]．

重症虚血心疾患に対する体外衝撃波治療法の開発は，厚生労働科学研究費補助金を得て実施している．治療法の詳細については，東北大学病院循環器内科のホームページを参照されたい(http://www.hosp.tohoku.ac.jp/department/cvi.html)．

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虚血性心疾患に対する体外衝撃波治療

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近年わが国では，人口の高齢化や生活習慣の欧米化に伴い，経皮的冠動脈インターベンション（PCI）や冠動脈バイパス手術（CABG）を施行できないようなびまん性狭窄病変をもつ症例など，従来の治療法では十分な治療効果を得られない重症例が増加してきており，新しい治療法の開発が期待されている．われわれは，培養細胞とブタ慢性虚血モデルを用いた基礎研究により，尿路結石破砕治療に用いられる出力の約10分の1という弱い出力の衝撃波を体外から虚血心筋に当てると，血管内皮増殖因子（VEGF）やその受容体であるFlt-1の発現が亢進すること，毛細血管数が増加して心筋虚血が改善すること，そして，それに伴い左室壁運動が改善することを確認した[1]．

これらの結果をもとに，狭心症症例に対して体外衝撃波治療の臨床試験を行っている．対象は，①20歳以上，②最大量の薬物治療に抵抗性で，かつPCIやCABGで完全な血行再建が不可能，③カナダ心臓病学会分類（CCS）でClass Ⅱ～Ⅳ，④負荷心筋シンチグラムや負荷心エコーで明らかな虚血領域を認める重症狭心症とした．心臓病治療専用に開発した衝撃波治療装置を用いて，装置に内蔵した超音波プローブを患者の前胸壁に当てて虚血部位に照準を合わせ，衝撃波を照射する．1カ所につき200発の衝撃波を，虚血領域の広さに応じて20～120カ所照射する．1回の治療時間は約3時間で，1日おきに3回治療を行う．痛みを伴わないため麻酔や鎮静は必要ない．2003年1月から重症狭心症患者9名を対象に実施した第1次臨床試験では，個人差はあるものの全例で胸痛の自覚症状が軽減し，またニトログリセリンの使用量が激減するなどの効果を認め，その効果は1年以上にわたって持続している[2]．自覚症状のみならず，負荷心筋シンチグラムで評価した心筋灌流も，衝撃波を照射した部位において改善を認めた[2]．一方，治療に伴う合併症や副作用は全く認めなかった．有効性をさらに客観的に評価するため，2005年11月から衝撃波治療とプラセボ治療を比較する第2次臨床試験が進行中である．さらにブタ急性心筋梗塞モデルにおいて慢性期の左室リモデリング抑制効果も認めたことから[3]，急性心筋梗塞症例に対する体外衝撃波治療も2007年2月から開始している．

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