Technology Brief

Update: Extracorporeal shock wave therapy for the treatment of angina

November 2011
This work is licensed under a Creative Commons Attribution Non-Commercial No Derivatives 2.5 Australia licence. In essence, you are free to copy and communicate the work in its current form for non-commercial purposes, as long as you attribute the authors and abide by the licence terms. You may not alter or adapt the work in any way.

For further information, contact the HealthPACT Secretariat at:
HealthPACT Secretariat
c/o Access Improvement Service, Centre for Healthcare Improvement,
Queensland Health
Floor 3, Forestry House
160 Mary Street, Brisbane QLD, AUSTRALIA  4000
Email: HealthPACT@health.qld.gov.au  Telephone: (07) 3234 0624.

For permissions beyond the scope of this licence contact: Intellectual Property Officer, Queensland Health, GPO Box 48, Brisbane Qld 4001, email ip_officer@health.qld.gov.au, phone (07) 3234 1479.

DISCLAIMER: This brief is published with the intention of providing information of interest. It is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements to health technologies. This brief is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

The State of Queensland acting through Queensland Health (“Queensland Health”) does not guarantee the accuracy, currency or completeness of the information in this report. Information may contain or summarise the views of others, and not necessarily reflect the views of Queensland Health.

This brief is not intended to be used as medical advice and it is not intended to be used to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. It must not be relied upon without verification from authoritative sources. Queensland Health does not accept any liability, including for any injury, loss or damage, incurred by use of or reliance on the information.

This brief was commissioned by Queensland Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers’ Advisory Council (AHMAC), reporting to AHMAC’s Clinical, Technical and Ethical Principal Committee (CTEPC). AHMAC supports HealthPACT through funding.

This brief was prepared by Mr Shamesh Naidoo and Ms Linda Mundy from the HealthPACT Secretariat.
TECHNOLOGY BRIEF UPDATE

REGISTER ID: WP090

NAME OF TECHNOLOGY: EXTRACORPOREAL SHOCK WAVE THERAPY FOR TREATMENT OF ANGINA

PURPOSE AND TARGET GROUP: PATIENTS WITH PERSISTENT ANGINA DUE TO ISCHAEMIC HEART DISEASE

2011 EFFECTIVENESS AND SAFETY ISSUES:

Since the 2010 prioritising summary, several studies have been published on the safety and effectiveness of extracorporeal shock wave therapy (SWT) for the treatment of angina and also as an angiogenic therapy\(^1\).

A double-blind crossover trial reported on the use of SWT in eight patients with severe angina pectoris who had already undergone coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) but had stable effort angina under intensive medication (age 70 ± 3 years) (level III-2 intervention evidence). The patient and treating doctor were blinded to the type of therapy delivered. Patients received a series of three treatment sessions in a week of placebo (SWT without irradiation) and after a 3-month “washout” interval they received three treatment sessions of SWT. No procedural complications or adverse effects were noted during or after therapy. Measurements taken three months following placebo treatment demonstrated a lack of improvement in symptoms and all other measurements including Canadian Cardiovascular Society (CCS) score, peak oxygen uptake (peak VO\(_2\)) and left ventricular ejection fraction. At 3-month follow-up, SWT was found to improve symptoms of angina as demonstrated by an improvement in the CCS score (\(p<0.005\)) and reduced nitroglycerin use (\(p<0.01\)). SWT also significantly improved the 6-minute walking distance and tended to improve both maximum exercise capacity and peak VO\(_2\) compared to baseline measurements (Kikuchi et al. 2010).

A small case series reported on the use of SWT in nine male patients aged 55 to 70 years (mean age 64) with coronary artery disease and stent implantation (level IV intervention evidence). Patients were hospitalised for either chest tightness, shortness of breath, or fatigue after stent implantation for earlier indications of myocardial infarction. SWT was applied to each ischaemic region over a 3-month period at 3-week intervals (for a total of 9 therapies per patient). Cardiac function and perfusion was assessed one month following the SWT treatment. One month after the SWT schedule, the researchers reported a significant reduction in the average CCS angina

\(^1\) A search was conducted using Ovid Embase with the term shock wave (explode and focus, and as a MeSH term) and the MeSH term cardiovascular disease (explode and focus), with limits applied to retrieve only English and human studies. 147 studies were retrieved, selected for further review by title and abstract inspection. A final selection of 9 papers were retrieved for data extraction.
class in patients from a baseline value of 3.0 to 2.0 \((p=0.035)\), and nitroglycerin use was also decreased. Cardiac systolic function was also improved after one month of treatment. No serious complications were reported (heart failure, bleeding, thrombosis, shock, death) and no pulmonary complications were reported during or after SWT. There was a significant decrease in the level of several enzyme markers (creatine kinase, creatine kinase MB, aspartate aminotransferase) and a maintenance of alanine aminotransferase levels, compared with pre-treatment levels, which was interpreted as evidence that SWT did not induce further damage to the liver or heart in these patients. Although these initial results appear to be favourable, no firm conclusions can be made as to treatment efficacy due to the small sample size, short time-frame for follow up and lack of control group. The researchers are planning a study with a longer term follow up (24 month) and a larger patient population using a drug-treatment comparator group (Wang et al. 2010).

Vasyuk et al (2010) reported a case series of 24 patients (average age 63.3 years) with ischaemic heart failure systolic dysfunction, who had experienced acute myocardial infarction (AMI) more than six months prior to enrolment (level IV intervention evidence). In addition, surgical revascularisation was not planned within the forthcoming six months. Patients were evaluated at baseline, three and six months. Shock wave therapy resulted in a significant decrease in CCS angina class from \(2.6 \pm 0.7\) to \(2.1 \pm 0.8\) \((p<0.01)\), with a significant decrease in nitroglycerin use from 2.0 to 1.0 uses per week at three months. This effect persisted to 6-months after SWT. No adverse events associated with the SWT procedure were reported (Vasyuk et al 2010).

An earlier case series which was unreported in the 2010 summary, described the results of 10 patients with chronic refractory angina pectoris (with no possibility of PCI or CABG) who were treated with SWT. Following delivery of nine SWT sessions over 3-months, the mean CCS class decreased from a baseline average of \(3.3 \pm 0.5\) to \(1.0 \pm 1.3\) at follow-up \((p=0.007)\). SWT was reported as being successful in six out of eight patients (75%), with myocardial perfusion improving only in the ischemic areas treated by SWT. It was noted that two patients did not achieve an improvement in objective measures (myocardial perfusion), despite reporting clinical benefit. The authors speculated that this improvement in angina symptoms may, in part, be considered to be a placebo effect. (Khattab et al 2007).

The 2010 prioritising summary noted that concerns had been raised regarding the safety of SWT (Jargin 2010) including unselective damage to cell membranes, the cytoskeleton and small vessels, which may contribute to the irreversible loss of muscle cells. In addition, concerns had been raised that endothelial damage by SWT may accelerate atherosclerosis. In a response to these concerns Holfeld et al (2010) provided evidence from histological analysis showing that cell membranes remained unharmed and nuclei showed no signs of hypertrophy, no cellular infiltrates in the interstitial space, or any kind of extravasates. This was displayed in a rat model over a
period of 14 weeks and was taken to be an indication for long-term stable benefit (Holfeld et al 2010). In response, Jargin further reiterated the point that a net benefit from SWT is not immediately understandable from the viewpoint of general pathology, and urges caution in widespread application of the technology (Jargin 2010).

2011 COST IMPACT:
Personal correspondence was received from the Medispec Asian market representative, stating that the unit cost of the SWT device is currently USD$150,000, which includes consumables for 20 initial patients to undergo an initial course of treatment of nine sessions over nine weeks. Included in this price is assistance with installation, three days operational, technical and clinical training, in addition to patient selection training, supervised treatments, and follow up visits for technical assistance. Currently Medispec has no distributor of the technology in Australia.

2011 SOURCES OF FURTHER INFORMATION:
Planned studies (other than Wang et al as mentioned earlier) have been identified on the clinicaltrials.gov register. Five studies (n = 28, 30, 60, 60, 60) were listed as all focusing on SWT for the treatment of refractory angina pectoris. Three of the five listed were randomised studies, with the remaining two being single group assignment studies. Estimated completion times ranged from August 2009 to July 2012. No studies identified in the literature search contained patient number enrollments that matched those on the register. Further monitoring for the eventual publication of the results of these studies is needed.

2011 SUMMARY OF FINDINGS
Whilst all of the above reported studies conclude that SWT is safe and effective, the studies have been performed on small patient groups with limited time-frame for follow up. The planned longer term studies and longer timeframes for follow up warrant continued monitoring of SWT as a treatment for angina and as an angiogenic therapy. Reviews and comments on the technology emphasise the need for more data from randomised, placebo-controlled trials before the widespread implementation of SWT for cardiovascular indications.

2011 HealthPACT ASSESSMENT:
As with the 2010 Brief written on this technology, included studies were of a low-level of evidence, on small groups of patients with a lack of long-term follow-up data. It is unlikely that this technology will be taken up by Australian clinicians in the short-term, therefore HealthPACT have recommended that information on this technology be noted and that no further research is warranted on extracorporeal shockwave therapy for angina at this time.
2011 LIST OF STUDIES INCLUDED

Total number of studies 4
  Level IV intervention evidence 3
  Level III-2 intervention evidence 1

2011 REFERENCES


PRIORITISING SUMMARY 2010

REGISTER ID: 000483

NAME OF TECHNOLOGY: EXTRACORPOREAL SHOCK WAVE THERAPY FOR TREATMENT OF ANGINA

PURPOSE AND TARGET GROUP: PATIENTS WITH PERSISTENT ANGINA DUE TO ISCHAEMIC HEART DISEASE

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- Yet to emerge
- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use
- Nearly established

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes ARTG number
- No Not applicable
- Not applicable

INTERNATIONAL UTILISATION:

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>LEVEL OF USE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials Underway or Completed</td>
</tr>
<tr>
<td>USA</td>
<td>✔️</td>
</tr>
<tr>
<td>Japan</td>
<td>✔️</td>
</tr>
<tr>
<td>Germany</td>
<td>✔️</td>
</tr>
<tr>
<td>India</td>
<td>✔️</td>
</tr>
<tr>
<td>Canada</td>
<td>✔️</td>
</tr>
<tr>
<td>Russia</td>
<td>✔️</td>
</tr>
</tbody>
</table>

IMPACT SUMMARY

Medispec Ltd provides Cardiospec™ which incorporates extracorporeal shock wave myocardial revascularisation (ESMR) technology with the aim of relieving chronic pain and improving quality of life for patients with severe ischaemic heart disease. The technology could be made available through existing infrastructure for patients who experience persistent angina for whom surgical treatment options have been exhausted.
2010 BACKGROUND

Ischaemic heart disease is the result of narrowing coronary arteries which supply blood to the muscle of the heart, or myocardium (Ito et al 2009). Atherosclerotic changes associated with lifestyle and other factors² contribute to this narrowing and decrease in blood flow, which in turn causes an imbalance between the supply and demand for oxygen to the myocardium. Myocardial ischaemia can cause temporary chest pain and reduced tolerance for physical exertion (‘angina pectoris’), permanent damage to the heart muscle (acute infarction), lethal arrhythmia and sudden cardiac death. Prognosis and quality of life for patients who have severe ischaemia/coronary artery disease and who are not indicated for surgery are poor. Often surgical options will have been exhausted, and alternative forms of effective treatment are lacking. Extracorporeal shock wave therapy (SWT), the generic term for ESMR™ technology, is emerging as a prospect for this application. SWT, which was first introduced 20 years ago as a fragmentising treatment for kidney stones, has been adapted as a non-invasive therapy for ischaemic heart patients (Ito et al 2009). The ESMR™ technology produces acoustic shock waves via a generator, supported against the patient’s chest by a water cushion. The generator produces an underwater spark at high-voltage (Figure 1), resulting in a high-amplitude pulse delivered to the appropriate area of the heart, as determined by ultrasound imaging (echocardiography) which locates and defines the extent of ischaemia. Several treatment sessions are required to obtain optimal results. No anaesthesia is necessary during the procedure.

² Factors include hypercholesterolaemia, hypertension, smoking, and diabetes.
The anticipated clinical impact of SWT is based on improved myocardial blood flow and enhanced angiogenesis. Increased blood flow after SWT is explained by nitric oxide, which is a potent vasodilator over short periods, while enhanced angiogenesis is thought to arise from up-regulation of vascular endothelial growth factors and their corresponding receptors, which has been observed after application of SWT (Jargin 2009).

2010 CLINICAL NEED AND BURDEN OF DISEASE

Ischaemic heart disease is a significant health outcome of cardiovascular disease (CVD), the major cause of mortality in Australia. CVD accounts for 34 per cent of all deaths nationally and causes a large proportion (18%) of the total disability adjusted life years in Australia. Potential years of life lost due to CVD in 2006 was estimated to be 191,600 person-years. The risk factors for CVD are smoking, high blood pressure, overweight, high cholesterol and low physical activity (BODCE 2007). It is estimated that CVD affects 3.7 million Australians, with 1.4 million suffering long-term disability due to these diseases (AIHW 2009).

In Australia, during the period 2006-07, there were 469,817 public hospital separations for diseases of the circulatory system. Of these, there were 162,328 separations for ischaemic heart disease (ICD code I20-25) (AIHW 2008). In New Zealand during 2002-03 there were 27,309 separations from public hospitals for ischaemic heart disease (ICD code I20-25) with a mean stay of seven days. In addition, there were 3,317 day cases for this indication (data supplied by the NZ Health Information Service).

2010 DIFFUSION

The technology has not yet diffused within Australia and New Zealand.

2010 COMPARATORS

Currently, management of ischaemic heart disease involves three main options. The first option is nitrate-based medication for which side-effects are common, including disabling headaches and dizziness. Continuous, long-term use of nitrates may lead to recurrent myocardial infarction (Thadani & Rodgers 2006). The remaining options are invasive procedures: percutaneous coronary intervention (PCI) which uses balloon dilation of narrowed arteries, and coronary artery bypass grafting (CABG) (Ito et al 2009).

2010 SAFETY AND EFFECTIVENESS ISSUES

Japanese researchers conducted clinical studies using SWT on a small group of patients with end-stage ischaemic heart disease (n=9), following promising results in experiments with pigs and rabbits (level IV intervention evidence). Patients (five men) were aged 55 to 82 years and not considered suitable for PCI or CABG, with a number having already exhausted these treatment options. SWT was administered
three times per week at intervals of one, three and 6 months. The treatments significantly reduced weekly use of nitroglycerin (p<0.01) and significantly improved Canadian Cardiovascular Society class scores compared to values obtained pre-treatment (mean scores > 2.5 and < 2.0, respectively; p<0.05). Of the six patients with a score of three, five had a score of two and one patient had class one angina after 12 months. Additionally, imaging with scintigraphy indicated that myocardial blood perfusion was enhanced in ischaemic areas treated with SWT. No adverse events or complications were noted (Ito et al 2009).

An abstract presented at the 20th World Congress of the International Society for Heart Research described a study which was conducted to assess the efficacy of SWT for post-bypass ischaemic patients (level IV intervention evidence). Seventeen patients underwent angiography which confirmed that PCI and CABG were no longer viable treatments. Ten of these patients had previous myocardial infarction and six had angina pectoris. The Cardiospec™ unit (Medispec Ltd) was used to deliver three treatments per week, every four weeks for a total of nine treatments. Scintigraphy was performed at one and three-month follow-up. Overall, ten patients had an improvement in their symptoms, while three patients had significantly improved myocardial perfusion at rest, as measured at three-month follow up (no p-values were provided in the abstract). No improvement in ischaemia was observed during exercise in these three patients. The significant improvements were observed only among the patients without history of myocardial infarctions, suggesting SWT is more appropriately indicated for angina without a history of myocardial infarction. No adverse events or worsening of symptoms were observed (Takayama et al 2010).

A German study presented at the World Congress of Cardiology, 2006, recruited 25 patients who had refractory angina (n=15) or chronic occlusion of one coronary vessel (n=10) (level IV intervention evidence). All patients, with a mean age of 64 years, were treated using with SWT using Cardiospec™ at the appropriate ischaemic zone and followed up after three months. Canadian Cardiovascular Society class scores improved from 3.22 ± 0.43 to 2.2 ± 0.68 (p<0.05) at the end of the three months. Exercise tolerance and myocardial perfusion were also significantly increased (Gutersohn et al 2006).

2010 Cost Impact

Medispec Ltd were contacted to provide information on cost of the Cardiospec™ unit, however no response was received.

2010 Ethical, Cultural or Religious Considerations

No issues were identified/raised in the sources examined.
2010 OTHER ISSUES

The sources examined in this summary provided evidence of statistical differences from baseline in outcomes for patients treated with SWT, but did not clearly define the clinical impact associated with these differences. On the basis of the Canadian Cardiovascular Society classification of angina definitions (Campeau 1976; SSCTS 2010) and the mean degree of change in this score from pre- to post-treatment, it would appear that improvement of angina symptoms, on an overall basis, is moderate in size. On a per patient basis, some patients would be expected to have had a large improvement in their symptoms, with corresponding ease in daily living activities.

Further information regarding the use of SWT for ischaemic heart disease is awaited in the results of a US trial presently being conducted in three US centres, however this trial also has a small patient sample (n=15, five per centre). Since SWT is usually intended for patients that are not amenable to alternative treatments for coronary artery disease, the best available evidence may be limited to studies that examine safety and efficacy.

A small randomised controlled trial (RCT) is currently being conducted by the Hadassah-Hebrew University Medical Center in Israel in conjunction with Medispec (ClinicalTrials.gov Identifier: NCT00662727). The trial commenced enrolment in 2008 and expects to be finalised by December 2010. Patients with refractory angina not amenable to revascularisation with angioplasty or bypass surgery (n=21) will be randomised to receive SWT or placebo, that is the same treatment but with no shockwaves delivered. The primary outcome is the total exercise time measured at six months follow-up and secondary outcomes are changes in stress-SPECT testing (to identify the ischemic areas) and angina pectoris Canadian Cardiac Society class also measured at six months.

A larger RCT (n=60) conducted by the Karachi Institute of Heart Diseases in conjunction with UNIQUIP INTERNATIONAL, Pakistan is ongoing but is no longer recruiting patients (ClinicalTrials.gov Identifier: NCT00776568). Patients with refractory angina pectoris were randomised to receive either anti-hypertensive drugs (ACE inhibitors, Ca channel blockers, beta blockers, diuretics, cholesterol lowering agents) or extra-corporeal shockwave treatment (low intensity shock waves applied as 300 shocks per visit for 9 visits at weeks 1, 5 and 9). The shock wave treatment aims to induce the growth and development of new vasculature in regions of severe ischaemia, perfusing areas unreachable by PCI and/or CABG). The primary and secondary outcomes measured at six month follow-up were the alleviation of angina symptoms and changes in stress-SPECT testing compared to baseline.

Concerns have been raised regarding the safety of SWT. Shock waves of sufficient power can injure cell membranes, small blood vessels and further contribute to ischaemia through the irreversible loss of cardiac muscle cells, which are incapable of mitosis (Jargin 2009). In the studies examined, no adverse reactions to SWT were
apparent, but longer term follow-up with larger patient samples may be necessary to substantiate the early safety outcomes of this technology.

2010 SUMMARY OF FINDINGS
Clinical studies of small sample size have been conducted on the basis of earlier promising results with animal studies for the application of SWT. It would appear that end-stage ischaemic heart disease patients who have exhausted other treatment options stand to experience at least moderate relief from symptoms of angina after a course of SWT with consequent improvement in daily living and less restrictions on physical activity. To date, the procedure has been shown to be safe within a 12 month follow-up period.

HEALTHPACT ASSESSMENT:
Although this assessment was based on low-level evidence with a lack of long-term follow-up data, several randomised controlled trials are expected to be completed and their results published in the near future. It would be prudent to await the results of these trials as shock wave treatment is considered an option of last resort for patients who have exhausted all other treatment avenues. HealthPACT have therefore recommended that this technology be monitored for further information in 12-months time.

NUMBER OF INCLUDED STUDIES

<table>
<thead>
<tr>
<th>Total number of studies</th>
<th>Level IV evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

2010 REFERENCES:


**2010 Search Criteria to be Used:**

Shockwave/shock wave therapy, angina  
Extracorporeal  
Ischaemic/ischemic heart disease, coronary artery disease  
Ischaemia, myocardium*