

WHAT'S NEW IN

General Medicine

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Introduction

The ancient Greek view of medicine based on the 'four humors' described by Galen and Hippocrates was replaced from the late 18th century onwards by the 'scientific medicine' proposed by the likes of Rudolf Virchow and Jean-Martin Charcot. This formed the basis for modern medicine and for the first time allowed true cure of many diseases. It wasn't until the 20th century, however, that the advances in the medical, pharmacological and surgical treatments of disease revolutionised medical practice. Since then, the development of scientific medicine has progressed at an almost exponential rate, bringing with it technological advances never thought possible a mere 20 years ago. This article highlights some of the most important and exciting new developments that have recently emerged in the four main subspeciality areas of medicine.

Cardiology

One of the most important advances in cardiology over the last 30 years has been the development of treatments to improve or restore patency in diseased coronary arteries. Since Andreas Gruntzig performed the first percutaneous transluminal coronary angioplasty (PTCA) in the late 1970s (1), the recurring problem with PTCA has remained that of re-stenosis, occurring in over 30% of patients after single vessel PTCA and over 65% in multivessel angioplasty (2). As a result PTCA often had to be repeated several times with implications for both healthcare economics and the patients psychological well-being, thereby diminishing its overall value.

The emergence of stainless steel self-expanding stents in the mid 1980s seemed initially to be an effective means of preventing vessel re-stenosis after PTCA and limiting the need for repeated angioplasty (2). Stent implantation however, was not without its own problems. Most stents were stainless steel and stent thrombosis was common (3). In an attempt to combat this, the early trials used intense anticoagulant regimes, which resulted in serious bleeding complications. Although these complications have largely been reduced by replacing the formal anticoagulant regimens with antiplatelet therapy, initially using aspirin and ticlopidine and more recently with aspirin and clopidogrel (4), the problems

associated with stent thrombosis after PTCA persist. Much of the last 10 years work has been aimed at solving this.

Glycoprotein IIb/IIIa receptor antagonists

Recently, the realization of the important role of platelets in thrombosis after coronary interventions has resulted in the introduction of platelet glycoprotein (GP) IIb/IIIa receptor antagonists. The benefits observed with GP IIb/IIIa antagonists used in conjunction with coronary intervention largely come from the results of the EPISTENT trial. This study randomly assigned 2,399 patients to stenting plus placebo, stenting plus abciximab (a GP IIb/IIIa inhibitor) or PTCA plus abciximab. All patients received heparin and aspirin, and the two stent groups also received ticlopidine. At 30 days, the rates of death, MI or urgent revascularisation were 10.8% in the stent plus placebo group, 6.9% in the PTCA plus abciximab group, and 5.3% in the stent plus abciximab group ($p < 0.001$) (5). As a result, the use of antiplatelet agents is now widespread, although the optimal antiplatelet and antithrombotic regime after stenting remains unclear. Common clinical practice, in part because of cost concerns, has reserved the use of GP IIb/IIIa antagonists for difficult or emergency cases rather than prophylactic use and favours clopidogrel over ticlopidine in addition to aspirin.

Drug eluting coronary stents

The most recent technological advances are in the development of vascular stents which enable local and systemic delivery of biochemical agents to reduce the rates of re-stenosis post procedure. They are referred to as "drug eluting stents". Insertion of these polymeric-coated stents results in delivery of medication directly to the site of vascular injury.

Following smaller pilot studies (6), the RAVEL trial used a stent which was coated in sirolimus (rapamycin), an immunosuppressive drug developed for the prevention of renal transplant rejection and a potent inhibitor of smooth muscle cell proliferation and migration. RAVEL randomised 238 subjects to either a sirolimus eluting stent (SES) or a bare metal stent. At 6 months follow up, the percentage of patients with $\geq 50\%$ stenosis in the SES

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group was 0% compared with 26.6% in the standard stent group ($p < 0.001$). In addition, the luminal diameter of the stented vessels was greater in the SES group than the bare metal stent group (7, 8). Further trials have also supported this data and go on to suggest that the results of using sirolimus-eluting stents are consistent across a broad range of patients including those with diabetes mellitus and small vessel disease (9).

Another study, ASPECT, investigated the effectiveness of drug eluting stents coated with paclitaxel. Paclitaxel inhibits cell processes that are dependant on microtubule turnover, including mitosis, cell proliferation and cell migration and in vitro, paclitaxel causes inhibition of smooth muscle cells and so theoretically could prevent neo-intimal hyperplasia of the vessel wall after angioplasty and stenting. The results of the ASPECT trial showed that paclitaxel eluting stents significantly reduced re-stenosis in the six months after intervention compared with standard stents (mean $[+/- SD]$, $14+/-21\%$ vs $39+/-27\%$; $p < 0.001$) (10), in line with the results from the RAVEL study.

Although the early results of drug eluting stents are promising, the long-term benefits and adverse effects are unclear. Unfortunately the economic impact of using these new stents must also be addressed given their high cost (US\$2900+ for sirolimus eluting stents), and some have questioned their cost effectiveness and value in the current healthcare environment (11). In a recent analysis of the cost effectiveness of drug eluting stents as part of the SIRIUS trial, 1058 patients were randomised to coronary revascularization with either a sirolimus eluting stent or a bare metal stent. Clinical outcomes, resource use and costs were assessed prospectively for all patients over a 1 year follow up period (11). Initial hospital costs were higher in the SES group due to the higher costs of the stents, but over the follow up period there were less repeat revascularization procedures after SES, significantly lowering the cost difference. Although at the end of the 1 year period the costs remained slightly higher for sirolimus stents, the benefits of fewer repeat procedures appear to outweigh this (11, 12). The continued development of these new stents seem set to have a beneficial effect both in terms of quality adjusted life years (QALY) from a patient perspective, and long term cost effectiveness to the health care system.

The Future

The pace of change in molecular biology in cardiology has now reached a new level. In the last year, new techniques have emerged which focus on the pathways of gene expression that precede events at the cell surface. Manipulating stem cells to either speed vascular endothelial injury repair, or to prevent damage in the first place may provide

one of the next avenues of therapeutic potential.

Summary

Although these new techniques in coronary revascularization are exciting, it must be remembered that they are not a cure for coronary artery disease and will not prevent the progression of atherosclerosis. Primary and secondary risk factor prevention remains of paramount importance.

Gastroenterology

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for over 100 years, since German chemist Felix Hoffman isolated acetylsalicylate (aspirin) for the Bayer Company in 1893. It was only in the 1970s, however, that NSAIDs were found to suppress inflammation by inhibiting the cyclooxygenase (COX) enzyme (13). Cyclooxygenase enzymes (also known as prostaglandin endoperoxide (PGH) synthase) catalyse the cellular conversion of arachidonic acid to prostaglandins, prostacyclins (PG) and thromboxane (TX) (14) (Figure 1) with the exact nature of the end product varying between cell types. Interruption of this process by NSAIDs limits the production of pro-inflammatory cytokines thereby limiting inflammation (15).

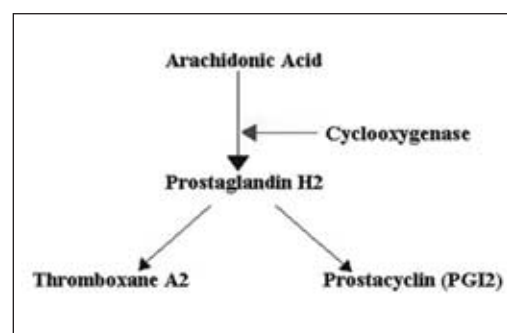


Fig 1. The role of Cyclooxygenase in prostaglandin synthesis

Selective NSAIDs

There are two isoforms of cyclooxygenase. COX-1 is produced constitutively in most tissues where it mediates physiologic functions such as gastric mucosal cytoprotection and regulation of platelet aggregation (16). COX-2 on the other hand is not normally expressed in most tissues but can be induced by a wide spectrum of growth factors and pro-inflammatory cytokines. Non-selectively blocking the COX enzymes, particularly COX-1, by NSAIDs accounts for the increased gastrointestinal side effects, such as bleeding, seen with these drugs; inhibition of COX-1 however, adds little to the anti-inflammatory effect of NSAIDs which appears to be mediated primarily by the COX-2 isoform. The selective blockade of the COX-2 enzyme, therefore, reduces the risk of gastrointestinal side effects whilst preserving the anti-inflammatory properties

of COX inhibition. Certainly in recent studies, selective COX-2 inhibition, even at high doses, was associated with a fourfold reduction in ulcers detected by 3 to 6 month endoscopy studies, when compared with normal doses of standard NSAIDs (17). In the VIGOR study, clinically significant ulcers were reduced by 54% in patients taking COX-2 inhibitors when compared with NSAIDs (18). As a result, COX-2 inhibitors are now important pharmacological treatments for arthritic and acute pain in individuals at high risk of gastrointestinal bleeding.

New uses for COX inhibitors

Cyclooxygenase inhibitors are now being proposed as a new treatment for the prevention and treatment of colorectal cancer (15, 19). COX-2, unlike COX-1, is induced by a wide spectrum of growth factors and pro-inflammatory cytokines and it is known that human tumours produce large quantities of prostaglandins, and COX-2 is over-expressed in many pre-malignant and malignant conditions, including colorectal adenomas and cancer, gastric cancer, Barrett's oesophagus and oesophageal cancer. There is also evidence of abundant COX-2 in oral leukoplakia, liver, lung, breast and pancreatobiliary system cancers (19, 20). Over-expression of COX-2 often correlates with a more aggressive course or worse prognosis and it appears to be involved in carcinogenesis by enhancing cellular proliferation and invasiveness, increasing immunosuppression and by its anti-apoptotic effects (15, 20).

Early observational studies linked the use of the NSAID, sulindac, with decreased adenoma formation in patients with Familial Adenomatous Polyposis (FAP). In 1983 Waddell and Loughry noted that a patient with FAP who was taking sulindac had a paucity of polyps on routine sigmoidoscopy (21). A number of trials looking at the use of NSAIDs in patients with FAP found that the number and size of polyps in people receiving sulindac decreased after 3 and 6 months treatment (22). Unfortunately when treatment was ceased the polyps returned, and there is some evidence that subjects developed colorectal cancer even when taking sulindac (19). The risk of GI side effects with long term NSAID use also caused concern. Nevertheless, these findings were important as it provided a theoretical means of delaying the need for colectomy in this condition. Using celecoxib, with an incidence of serious GI side effects half that of standard NSAIDs (15), Steinbach (16) studied the effect of a selective COX-2 inhibitor on colorectal polyps in patients with FAP. 77 patients were randomly assigned to celecoxib or placebo; after 6 months of celecoxib treatment there was a 28% reduction in the mean number of colorectal polyps ($p=0.003$) and a 30.7%

reduction in the polyp burden (the sum of polyp diameters) ($p=0.001$). Importantly, there were no significant differences between the treatment group and placebo group in terms of adverse events (16). The result of the trial led the US Food and Drug Agency (FDA) to approve celecoxib as a treatment for FAP.

Rofecoxib was, until recently, the other mainstream COX-2 inhibitor. This drug did not carry a license for use in colorectal disease, but in 2000 the APPROVe study was started as a multicentre, randomised, placebo controlled trial to determine the efficacy of rofecoxib treatment on the recurrence of neoplastic large bowel polyps in patients with a history of colorectal adenomas, in an attempt to bring it in line with celecoxib usage. 2,600 patients were enrolled and randomised to rofecoxib or placebo. Unfortunately, data at 18 months follow up revealed an increased relative risk for adverse cardiovascular and thrombotic events in the COX-2 arm of the study. The relative risk of these events in patients taking rofecoxib versus placebo was 1.96 (95%CI 1.20, 3.19; $p=0.007$). As a result, on 30th September 2004 the manufacturers withdrew rofecoxib from the worldwide pharmaceutical market (see the Committee on Safety of Medicines at www.mca.gov.uk). This has not been the first time that the safety of rofecoxib has caused concern; in the VIGOR study (18), there was an increased risk of acute myocardial infarction in the patient group taking rofecoxib although this did not reach statistical significance.

The withdrawal of rofecoxib has not yet affected the other COX-2 inhibitors on the market although there are concerns whether the cardiovascular side effects seen with rofecoxib may also occur with the other COX-2 inhibitors as a "class effect". There is some evidence to dispute this (23) and celecoxib retains its US license as a treatment for FAP. Currently in the UK, celecoxib does not carry a license for use in colorectal disease.

Until its withdrawal, rofecoxib was being investigated as part of the VICTOR study, a clinical trial to study the effect of this drug in patients with colorectal cancer who have had potentially curative resection of the tumour. The primary hypothesis being that rofecoxib administered for 2 years will result in greater overall survival compared with placebo. The first results were expected from this trial in 2009 (24). It now remains to be seen whether this trial will be adjusted to study one of the alternative COX-2 inhibitors.

The Future

Combining COX-2 inhibitors with radiotherapy may also become a recognised treatment for cancer. Prostaglandins protect cells from irradiation injury, and this protective mechanism within neoplastic cells

could theoretically be halted by the use of COX-2 inhibitors. This idea is currently under investigation in three trials: celecoxib plus irradiation in medically inoperable Stage I non-small cell lung cancer, (NSCLC)(20), celecoxib and radiotherapy in intermediate prognosis NSCLC (20) and celecoxib with cisplatin chemotherapy in advanced oesophageal cancer (25). There are also many studies trialing COX-2 inhibitors with chemotherapy alone (20).

Summary

In the UK, the use of COX-2 inhibitors is widely accepted in the treatment of osteo- and rheumatoid arthritis and also in the management of acute musculoskeletal pain. There is sufficient enough data supporting the use of COX-2 inhibitors in pre-malignant bowel conditions such as Familial Adenomatous Polyposis, that celecoxib has a licence for this indication in the USA. Although not the case in UK, intense media interest (BBC News August 2001) may well result in similar licensing here. However the concerns over safety data for COX-2 inhibitors, leading to the withdrawal of rofecoxib, continue to overshadow their use. Further evidence is required to see whether the adverse events are limited to just that particular drug, or whether they are a class effect of COX-2 inhibitors. Nevertheless, pre-clinical trials continue to suggest that selectively inhibiting COX-2 enzymes may be a useful approach to treating many malignancies including colorectal cancer.

Neurology

Stroke is one of the leading causes of mortality in the world and the leading cause of disability in the western hemisphere (26, 27). The cost to the healthcare system after surviving a stroke has been estimated at US\$35-50 000 per year (28). It is not surprising, therefore, that an effective therapy for this condition is desperately needed.

Up to 85% of all strokes are ischaemic and are mostly caused by embolic occlusion of a cerebral artery leading to a reduction in cerebral perfusion and, within minutes, to ischaemic infarction. At the centre is an area of irreversibly damaged brain tissue, and surrounding this is an area of hypoperfused, but still viable tissue called the penumbra (28). It is this area of viable brain tissue which can be saved if rapid therapy is able to restore blood flow. The systemic delivery of intravenous thrombolytic agents has emerged as a treatment which may address this problem. The use of thrombolysis in acute ischaemic stroke (AIS) appears to provide a superior outcome compared to standard therapy.

Thrombolysis for stroke

It has been nearly 10 years since the National Institute of Neurological Disorders and

Stroke (NINDS) published a study which demonstrated the efficacy of using intravenous recombinant tissue plasminogen activator (rtPA) for the treatment of acute ischaemic stroke (29). Although the NINDS trial was small, its major treatment effect resulted in a statistically significant result equivalent to 120 more independent survivors per 1000 treated (29, 30).

In addition to the NINDS trial, in 1995 the European Cooperative Acute Stroke Study (ECASS) I was published, also looking at the efficacy of rtPA. This was followed by ECASS II in 1998 and ATLANTIS in 1999. These four studies randomly assigned a total of 2775 patients to treatment with placebo (n=1384) or iv rtPA (n=1391). The therapeutic window for treatment after the onset of symptoms was set at 0-3 hours (NINDS), 3-5 hours (ATLANTIS) or 0-6 hours (ECASS I and II). All four studies required a baseline CT scan to exclude intracerebral haemorrhage (ICH). The results of these trials, and in particular the NINDS trial, led to the US FDA approving the use of rtPA within 3 hours of onset of an acute ischaemic stroke (28).

More recently, Wardlaw *et al* (31) performed a meta analysis of all randomised trials of thrombolysis in stroke regardless of time windows, dosage, administration route and substance. The objective was to show that thrombolysis reduced the risk of late deaths from stroke and that the benefits in outcome of thrombolysis outweighed the early hazards of intracerebral haemorrhage. Although symptomatic and fatal ICH were significantly more common as a result of thrombolysis ($p < 0.000001$), thrombolysis administered up to 6 hours after ischaemic stroke significantly reduced death or dependence at the end of follow up ($p = 0.0015$). This is equivalent to 44 fewer deaths per 1000 treated. When treatment was given within 3 hours after the onset of stroke, there was an even greater risk reduction for death or dependency ($p = 0.00001$), equating to 126 fewer deaths or dependant patients per 1000 treated. The difference between the benefit of rtPA in the 0-3 h window or the 3-6 h window was not significant, but showed a trend towards better improvement with earlier therapy (28, 31).

Their conclusions were that the significant increase in early death and non-fatal ICHs are offset by the significant reduction in disability in survivors after thrombolytic treatment. There was also a negative correlation between outcome and the time to treatment with thrombolysis, leading to phrases such as "lost time is lost brain" or description of acute stroke as a "brain attack" hinting at the need for prompt treatment.

Current Situation

Unfortunately, despite being heralded as the new standard of care for acute stroke, the use

of rtPA is still highly controversial. In the USA, some series report that only 1% of all ischaemic stroke patients and 2% of time-eligible (3 hour window) patients are thrombolysed, rates which are pitifully low for a country which approved the use of rtPA in AIS nearly 10 years ago (28). In the UK, the use of thrombolysis to treat acute ischaemic stroke tends to be limited to teaching hospitals and tertiary referral centres; its use in District General Hospitals (DGH) is rare (30). The limited use of this treatment seems to stem from the controversies surrounding the safety and applicability of rtPA. Not only does the use of thrombolysis in stroke require adherence to strict protocols as deviations from these are associated with poor outcomes (27), but the protocols require access to a wide range of associated services. In particular neurological and neuro-imaging resources need to be rapidly and continually available and the health care infrastructure at DGH level in the UK is presently at odds with the short assessment and treatment windows necessary for this treatment (32).

In a further attempt to address the concerns about the safety of rtPA in stroke, Graham (33) performed a meta-analysis of 15 open-label studies (2639 patients) that reported the standard use of rtPA. ICH occurred in 5.2% of patients, which was lower than that found in the NINDS trial, whilst clinical outcome and mortality were comparable. Regardless, the use of thrombolysis in AIS remains limited in the UK. Further trials are currently underway to examine the safety and efficacy of rtPA. ECASS III is a European study looking at rtPA beyond the 3 hour time window – a situation more representative of patient presentation in UK. The Third International Stroke Trial (IST-3) is an international multicentre randomised control trial based on the NINDS trial but with a time window extending up to 6 hours from onset of stroke (30). It aims to recruit up to 6000 patients from both teaching and district general hospitals and the results from this trial are not expected until 2009 (see www.dcn.ed.ac.uk/ist3). In addition, a European registry for rtPA in ischaemic stroke has been established. Any patient who receives treatment for stroke with rtPA within 3 hours must be reported (see www.acutestroke.org).

The body of evidence supporting the use of thrombolytic agents in AIS is growing despite the reservations from some clinicians. The National Service Framework (NSF) for Older People has provided a clear mandate to improve stroke care by facilitating the development of a thrombolysis service for patients with AIS. This should be provided by the implementation of specialist stroke units in hospitals. In 1999, only half of all UK patients with stroke had access to a

stroke unit (30), whereas the NSF standard is that every general hospital should have a stroke unit by the end of 2004. Stroke unit care undoubtedly saves lives. If adequately resourced, it leads to 50-60 extra survivors per 1000 treated (30), and the use of thrombolysis in these units will improve survival further.

The Future

Intra-arterial thrombolysis delivered directly on to a vessel occlusion has only been trialled in two studies (Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II) in the USA. Although the rates of intracerebral bleeding may be higher, there are suggestions that recanalization rates are better with intra-arterial thrombolysis even up to 6 hours (28, 34). These trials however did not satisfy the FDA sufficiently to gain approval for use in the USA and within the UK such therapy would be almost impossible to deliver as it requires round the clock interventional neuroradiology services. Despite this, PROACT III is planned.

Another promising new development is the combination of thrombolysis with the use of glycoprotein IIb/IIIa antagonists (GP IIb/IIIa) in the hope that this might improve vessel patency rates in line with cardiological studies. The results of pilot studies of the Safety of Tirofiban in Acute Stroke (SATIS) trial were published in March 2004 (35) and suggest a favourable outcome when reduced-dose rtPA thrombolysis is combined with a GP IIb/IIIa antagonist. Full scale randomised controlled trial results are needed.



Fig 2. Transcranial doppler applied as a head-frame. In clinical practice the patient would be supine if receiving combined TCD and thrombolysis.

A further adjunct to rtPA thrombolysis is the addition of ultrasound enhancement. Low KHz frequencies applied via transcranial doppler (TCD) (Figure 2) are known to potentiate rtPA effects but can cause intolerable side effects, such as tinnitus, in some patients. Higher frequencies however, in the order of 1–2.2 MHz frequencies can also enhance TPA-induced thrombus dissolution and this frequency

range is commonly used for diagnostic and monitoring procedures without problem. The CLOTBUST trial has recently published Phase I trial data showing that rtPA in ischaemic stroke when combined with 2 MHz TCD provides superior recanalization to rtPA alone (28, 36, 37). Full trial data are pending.

Summary

Thrombolysis is an effective therapy for ischaemic stroke whether performed intravenously within 3 hours or intra-arterially within 6 hours. Sadly, the use of thrombolysis for this condition is underused not only in the UK, but internationally. The National Service Framework for Older People (section 5) has highlighted this as an area which needs attention, but the debate over safety is delaying implementation. The critical issue, it seems, in introducing this service in UK hospitals is the creation of an infrastructure of acute stroke teams, stroke units and neuroradiology services.

Respiratory Medicine

Chronic Obstructive Airways Disease (COPD) is one of the leading causes of mortality and morbidity worldwide and is characterised by airflow obstruction that is progressive, not fully reversible and does not change markedly over several months (www.nice.org.uk [Feb 2004]). The burden on the NHS is huge; in 1996 the direct cost of COPD in the UK was approximately £490 million (38). Treatment options for COPD are usually aimed around halting the progression of the disease, preventing and shortening exacerbations, and improving exercise tolerance and survival. These treatments revolve around inhaled bronchodilators and corticosteroids. Despite this, the only therapy that has been shown to alter the rate of progression of COPD is cessation of smoking (39).

Lung Volume Reduction Surgery

The treatments for COPD improve lung function, but many patients still remain intolerably breathless. One method of treating severe COPD is to remove areas of poorly functioning lung in order to improve symptoms and lung function, and is known as Lung Volume Reduction Surgery (LVRS) (40). The underlying principle suggests that by removing hyperinflated, poorly functioning lung the remaining lung fits better to the ribcage with improvements in the mechanics of breathing. In hyperinflated COPD chests the diaphragm is both flattened and shortened limiting muscle performance. Reducing hyperinflation allows the diaphragm to lengthen and approximate to its original shape, increasing its area of apposition with the chest wall and improving its mechanical performance (41, 42). LVRS has also been shown to improve right

ventricular cardiac function in patients with severe emphysema (43).

The NETT study (44), an important risk-benefit assessment of this treatment, was published recently. It randomised 608 patients with severe emphysema to LVRS and 610 to medical therapy. The results showed that LVRS is associated with a greater chance of improvement in exercise capacity, lung function, quality of life and dyspnoea. It also demonstrated a survival benefit in carefully selected patients with predominant upper lobe heterogeneous emphysema (44). The major limiting factor with LVRS, however, remains the potential for major morbidity and mortality following surgery. Although the NETT study data outlined acceptable rates of surgical mortality and morbidity, the risks of surgery remain high even with thoracoscopic approaches.

Alternatives to LVRS: Endoscopic Lung Volume Reduction

The risks and side effects of traditional thoracic surgery led to the concept of reducing lung volume using minimally invasive techniques; this would replicate the benefits of LVRS but reduce the risks and recovery periods from open surgery (45).

One approach is to block air entry into a lobe or segment of emphysematous lung resulting in collapse of this area and reduction in volume. Various methods have been studied including sealing the airways with glue, plugging the airways or by insertion of one-way valves. An alternative approach to reducing hyperinflation in COPD is to create low-resistance extra-anatomical tracts between the emphysematous segments of lung and proximal airways. This, in theory, would allow trapped air to escape by bypassing the small airways which tend to collapse during expiration (46).

Airway Occlusion

One of the first groups to try endoscopic airway occlusion published their experience in 2003 (47). They studied 5 males and 3 females and initially inserted detachable silicone balloons into airways to occlude the lumens. These were subsequently found to be unacceptable due to balloon migration and were replaced with stainless steel wire struts containing a bio-compatible sponge. The results were promising, with 5 patients recording improvements in dyspnoea, exercise tolerance and quality of life with no evidence of strut migration.

More recently, a specific one-way endobronchial valve has been designed (Emphasys Endobronchial Valve; Emphasys Medical; Redwood City CA, USA) (Figures 3 and 4). This valve is designed for insertion into target bronchi to promote atelectasis by preventing airflow into the bronchus whilst

allowing air and mucus to escape, theoretically avoiding the risks of post-obstructive pneumonia. The net result of this system is collapse of the target emphysematous lung segments, and redirection of air flow (or ventilation) to the healthier areas of lung (48). The valve can be inserted into the intended bronchus via a fibre-optic bronchoscope in a manner similar to stent insertion - it can also be removed if necessary with biopsy forceps (45). Toma *et al* recently published the first data on clinical experience with this device (49). They studied 8 patients with median FEV1 of 0.79L (range 0.61-1.07; 23.7% of predicted). Four weeks after stent insertion, the FEV1 in two patients had improved by 80-100%. Only 4 of the patients however, had radiographic signs of atelectasis. There was no evidence of post-obstructive pneumonia and no patients died. Despite the lack of lobar collapse in every patient, there was a statistically significant improvement in pulmonary function, especially in transfer factor (TLCO). Similarly, in a pilot study by Snell *et al* (50) trialling Emphasys valves in 10 patients with apical emphysema, there was a significant improvement in gas transfer from 7.47 (+/- 2.0) to 8.26 (+/- 2.6) mL/min/mm Hg ($p=0.04$) (50).

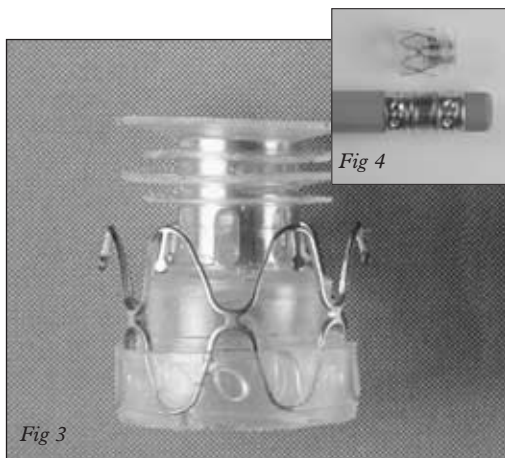


Fig 3. The Emphasys Endobronchial Valve

Fig 4. Actual size of the Emphasis Endobronchial Valve

The failure to cause complete collapse in some patients in both studies was probably attributable to the excessive collateral flow found in emphysematous lungs. There is little in the way of collateral ventilation in the normal human lung, but studies have shown that collateral ventilation occurs to a much greater extent in emphysema (51). In addition, the improvement in TLCO in these studies and in a further study by Yim *et al* (48) suggests that post procedure, airflow could be redistributed via the collaterals towards healthier portions of the lung thereby reducing V/Q mismatch and decreasing the physiological dead space. It would seem, therefore, that striving to achieve complete collapse of the target lung lobe may not be essential, and as a result of

these pilot studies, a large randomised control trial of the Emphasys valves has recently been approved in the USA.

Another new endobronchial valve for lung volume reduction has been developed (Spiration Intra-Bronchial Valve, Spiration; Redmond, WA USA) (Figures 5 and 6). It is an umbrella shaped device consisting of a polyurethane membrane on a nitinol frame. By having the convex side positioned distally in the airway, mucus and air can escape from the target bronchus whilst air is prevented from entering (45). It is also suitable for bronchoscopic placement.

Use of Airway Sealants

Alternative methods of bronchoscopic lung volume reduction rely on disrupting surfactant function and then sealing the airways at the target region with "tissue glue"; atelectasis of the target area of lung can then be achieved. This method has been tested in a animal study by Ingenito *et al* (52), and produced atelectasis and scarring in 55% of the treated sites. Unfortunately it was associated with the development of sterile abscesses at 3 of the 11 target zones making it unsuitable for clinical use (52).

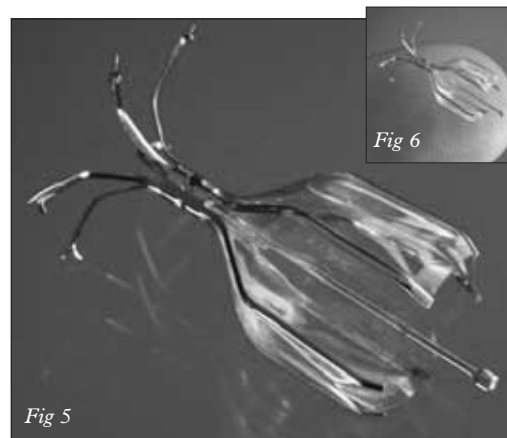


Fig 5. Spirations/Intra-Bronchial Valve.

Fig 6. Actual Size of the Spiration Intra-Bronchial Valve.

Following this, the same group incorporated bioengineering principles into their procedure, aiming to mimic normal scar formation at the target site by using an enzymatic primer solution to remove epithelial cells from the target region and a modified hydrogel scaffold to promote healing and scarring. This would produce target areas of persistent atelectasis without abscess formation (46, 53). The results in a papain-induced sheep model of emphysema, showed a reduction of lung volume in 33 of 36 target areas (53). The 3-week post-procedure physiological measurements revealed a significant decrease in the total lung capacity, functional residual capacity and residual volume (52). There was no pleural effusion or abscess formation at any of the target sites.

The primary advantage of this method is its similarity to the broncho-alveolar lavage

techniques familiar to all physicians who perform bronchoscopy. Ingenito's work raises the possibility of using the same techniques in humans, but human data is still awaited.

The Future: Bronchial Fenestration

Future developments in bronchoscopic LVRS techniques include the creation of extra-anatomical pathways between lung parenchyma and large airways. This would improve expiratory collateral flow from hyperinflated areas of the lung, bypassing the flow-limiting segments of the emphysematous airways. In 2003, Lausberg *et al* (54) published their results of this procedure on twelve human emphysematous lungs removed at the time of transplant operation. The lungs were placed in an airtight ventilation chamber and a forced expiratory manoeuvre simulated. Flow and expired volume from the bronchial stump were measured continuously. A bronchoscope was then inserted and using a radiofrequency catheter, passages were created through the wall of three separate bronchi into the adjacent lung parenchyma. Expandable stents were placed in these passageways to maintain patency. The results of this study showed that creation of these extra-anatomical broncho-pulmonary passages caused an increase in FEV1 from 245 +/- 107mL to 447 +/-199 mL ($p < 0.001$) (54). These promising results led to Rendina *et al* (55) testing this principle on in-vivo lungs. After thoracotomy, but prior to removal of the lung or lobe in patients undergoing transplant or open LVRS operations, extra-anatomical passages were created between the pulmonary parenchyma and segmental or sub-segmental bronchi. There were no significant adverse effects in any patient and confirmed that the procedure is feasible in human subjects; clinical trials can now follow.

Summary

The concept of non-resectional LVRS appears to be a highly promising therapeutic approach to severe emphysema with several strategies now available. The results from the pilot studies are encouraging and continued research and development in this area suggests that endoscopic treatments may prove to be a successful and widely applicable tool for treating COPD.

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