HEART FAILURE

Cardiac transplantation: indications, eligibility and current outcomes

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INTRODUCTION

Despite advances in medical and device therapy, the prognosis and quality of life of patients with advanced heart failure (HF) remains poor. For a carefully selected group of these patients, cardiac transplantation is the treatment of choice.

The first human-to-human heart transplant was performed in Cape Town on 3 December 1967 by Christiaan Barnard; the patient died 18 days later of infective complications. Outcomes were poor in the early years, but with the discovery of ciclosporin in the 1980s there was an improvement in survival which led to a peak in cardiac transplant activity in the early 1990s.1

Between 1993 and 2004, there was a reduction in the number of cardiac transplants reported to the registry of the International Society for Heart and Lung Transplantation (ISHLT); however in recent years, the numbers reported have grown to >5000 annually worldwide.1 With increasing numbers of patients now referred for consideration of transplantation, a significant imbalance between numbers of patients referred for consideration of transplantation, a significant imbalance between supply and demand exists.2,3 There are more candidates, and patients are increasingly complex, older,3 on mechanical circulatory support pretransplant and increasingly sensitised.1

INDICATIONS FOR HEART TRANSPLANTATION

Heart transplantation is the treatment of choice for selected patients with advanced HF who have limiting symptoms despite optimal conventional treatment and evidence of a poor prognosis. The limited number of available donor hearts restricts this treatment to a small fraction of potential recipients. Allocation of a scarce resource (the donor heart) requires two different perspectives. One is the risk and benefit for the individual patient. The second is the patient’s capacity to benefit, relative to the wider pool of potential recipients. Careful selection is crucial to ensure best use of this resource.

Heart transplantation is generally considered when it is likely to improve quality of life and increase survival. Box 1 lists the indications for the referral of ambulatory patients with chronic HF and the indications for urgent inpatient assessment.

Assessment prior to listing for heart transplantation

Ambulatory patients are usually evaluated over a 2–3 day period during which they meet members of the transplant team and receive education and information about the risks and benefits of heart transplantation. Evaluation includes investigations to assess prognosis and importantly identify potential contraindications. Box 2 lists the common tests performed as part of transplant workup. This list is not exhaustive as investigations are individualised. Hospitalised patients, such as those with decompensated chronic HF and those in cardiogenic shock, may also be evaluated for heart transplantation. For these patients, the evaluation process will depend on their clinical state and fitness to undergo investigations. To arrive at a decision about suitability for listing all cases are discussed by a multidisciplinary team at the transplant centre.

Imaging

Echocardiography provides information on the potential aetiology of HF, assessment of biventricular function, presence or absence of associated valvular lesions and an estimation of pulmonary artery systolic pressure. In patients who may require a left ventricular assist device (LVAD) as a bridge to transplantation, particular attention is given to right ventricular structure and function, aortic valve competence and exclusion of a communication across the interatrial septum. In the current era, many patients have undergone additional imaging such as coronary angiography, cardiac MRI and/or cardiac CT.

Functional capacity

Objective assessment of functional capacity confirms or refutes a patient’s perception of exercise limitation and provides prognostic information. Cardiopulmonary exercise testing involves a bicycle or treadmill exercise test with continuous measurement of ventilation and gas exchange. Achievement of the anaerobic threshold or a respiratory exchange ratio (RER) of >1.05 implies near-maximal exercise. In patients who achieve maximal exercise, a peak oxygen uptake (peak VO₂) of <10mL/kg/min is a strong predictor of poor prognosis.4 Patients taking beta-blockers with
Box 1 Indications for referral of ambulatory patients with chronic heart failure

1. Patients on optimal medical therapy who have limiting symptoms on exertion.
2. Patients who require frequent admission to hospital (two or more in 12 months) despite adequate therapy and adherence.
3. Deteriorating renal function or inability to clear congestion without adversely affecting renal function.
4. The need to decrease the dose of stop prognostically beneficial medication due to symptoms (often hypotension), or side effects like renal dysfunction.
5. Worsening right ventricular function or rising pulmonary artery pressure.
6. High or rising natriuretic peptide levels despite optimal therapy.
7. Frequent episodes of ventricular arrhythmia despite optimal drug and electrophysiological therapy.
8. Anaemia, weight loss, hyponatraemia, liver dysfunction attributable to heart failure.

Indications for urgent inpatient referral

1. Inability to wean inotropic therapy.
2. Need for percutaneous mechanical circulatory support to treat a patient in cardiogenic shock.
3. Ventilatory support with use of positive airway pressure for intractable pulmonary oedema.
4. Refractory ventricular arrhythmia.

(All in the absence of a contraindication to heart transplantation)

a peak VO₂ <12 mL/kg/min, or peak VO₂ <14 mL/kg/min if unable to tolerate a beta-blocker, are considered appropriate for cardiac transplant candidacy. Cardiac resynchronisation therapy (CRT) may improve New York Heart Association class and 6-minute walk (6MW) distance but CRT does not affect the predictive value of peak VO₂ on adverse cardiac events. In young patients (<50 years) and women, per cent of predicted peak VO₂ (<50%) can also be used to guide transplant candidacy in conjunction with peak VO₂. Furthermore, in patients unable to achieve a maximal test (RER <1.05), a minute ventilation/carbon dioxide production slope >35 is an additional marker of adverse prognosis. Although distance covered during 6MW test is a simple method for quantification of exercise intolerance in patients with HF, it is not a surrogate for peak VO₂ in assessing prognosis in advanced HF.

Right heart catheterisation

Right heart catheterisation (RHC) is mandatory for transplant assessment, and is periodically repeated (usually every 3–6 months) in patients on the waiting list. RHC allows direct measurement of right atrial pressure, pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PA) and mixed venous oxygen saturation. The cardiac output (CO) is also measured by either thermodilution and/or the modified Fick method. Transpulmonary pressure gradient (TPG) and resistance in both systemic and pulmonary vascular beds can then be calculated.

Elevated filling pressures despite optimal treatment are associated with a poorer prognosis.

Biomarkers

Natriuretic peptide levels are predictive of prognosis in those with advanced HF. A well-treated patient with high N-terminal pro B-type natriuretic peptide (NT-proBNP) is likely to require cardiac transplantation in the ensuing 12 months. In practice, we have found that patients with advanced HF and a suppressed NT-proBNP of <750 pg/mL are highly unlikely to die or require urgent heart transplantation or mechanical circulatory support in the subsequent 2 years.

Heart failure prognostic scores

The Seattle Heart Failure Model (SHFM) and the Heart Failure Survival Score (HFSS) are the most widely used risk scores in the advanced HF population. These provide additional information regarding prognostication during assessment. Estimated 1-year survival <80% in the SHFM is regarded as a reasonable cut-off to consider transplant listing, but the SHFM tends to overestimate survival in younger patients with advanced HF and sensitivity is extremely limited. Transplantation can generally be deferred in the low-risk group (score ≥8.1, 1-year survival 93%) when using HFSS.

Allosensitisation

Allosensitisation to human leucocyte antigens (HLA) may occur in women who have been pregnant or patients who have received allogeneic material, such as a blood transfusion or transplant. Allosensitisation can impact on the chances of successful donor-recipient matching and is factored into the timing of listing for a heart transplant. Further details can be found in the referenced reviews on this subject.
Education in Heart

Box 3  Contraindications to cardiac transplantation

► Active infection (patients with chronic viral infection such as hepatitis B, hepatitis C and HIV may be considered if viral titres are undetectable on treatment/following treatment with no evidence of other organ damage).
► Symptomatic cerebral or peripheral vascular disease.
► Diabetes mellitus with end-organ damage, eg, nephropathy, neuropathy, proliferative retinopathy. Poorly controlled diabetes with glycosylated haemoglobin persistently >7.5% or 58 mmol/mol is a relative contraindication.
► Current or recent neoplasm: risk of recurrence should be discussed with the oncologist.
► Severe lung disease: FEV₁ and FVC <50% predicted or evidence of parenchymal lung disease.
► Irreversible renal dysfunction with estimated glomerular filtration rate <30 ml/min/1.73 m².
► Irreversible liver dysfunction, eg, cirrhosis.
► Recent pulmonary thromboembolism (generally in the last 3 months).
► Pulmonary hypertension with pulmonary artery systolic pressure >60 mm Hg, transpulmonary gradient ≥15 mm Hg and/or pulmonary vascular resistance >5 Wood units. If irreversible with either pharmacological manipulation or mechanical unloading of the left ventricle, then this is an absolute contraindication to isolated heart transplantation.
► Psychosocial factors including history of non-compliance with medication, inadequate support, ongoing/recent drug or alcohol abuse, current smoker.
► Obesity (body mass index >35 kg/m² or weight >140% of ideal body weight).
► Other multisystem disease with poor long-term survival. FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

CONTRAINDICATIONS

Box 3 lists some of the common contraindications to heart transplantation. Many of these are relative, potentially reversible and should be considered in the context of each patient’s clinical need, capacity to benefit, availability of donor organs in a healthcare system and the opportunity cost for other potential recipients.

Age

The number of patients above the age of 60 years being transplanted has increased over the past 10 years. Furthermore, in the recent era, 5-year survival in carefully selected septuagenarians is similar to those aged 60–69 years. However, 5-year mortality in those aged ≥70 years (29.3%, 95% CI 28.5% to 30.2%) is poorer compared with those aged 18–59 years (26.9%, 95% CI 26.4% to 27.4%). Recipients aged ≥70 years are less acutely ill, have fewer comorbidities and less likely to have durable LVAD support before transplantation.

Pulmonary hypertension

The combination of PA systolic pressure >60 mm Hg, TPG (mean PA pressure – mean PCWP) >15 mm Hg and Pulmonary Vascular Resistance (PVR) (TPG/CO) >5 Wood units is a relative contraindication to listing. This is due to the risk of acute right HF from insufficient accommodation of the donor heart to a high PVR. Testing for reversibility of pulmonary hypertension may be performed using intravenous nitroglycerin or sodium nitroprusside if PA systolic pressure ≥50 mm Hg, in combination with either TPG ≥15 or PVR ≥3 Wood units, while maintaining a systolic arterial blood pressure ≥85 mm Hg. If unsuccessful, hospitalisation for a prolonged attempt at reversibility (usually up to 48 hours) using diuretics, inotropes and vasodilators can be tried.

In those failing pharmacological manoeuvres, mechanical unloading of the left ventricle using a durable LVAD has been shown to reduce PVR in patients with pulmonary hypertension secondary to left heart disease. Such patients may then be eligible for heart transplantation.

Renal dysfunction

Renal dysfunction is frequently encountered in patients with advanced HF. This is often as a result of low CO and/or renal venous congestion. Intrinsic renal disease may be excluded with ultrasound examination and estimation of proteinuria. Occasionally in a euvolemic patient without evidence of intrinsic renal disease and a short history of renal dysfunction, it may be appropriate to evaluate the effect of increasing CO with intravenous inotropic therapy. A significant improvement in renal function may permit listing for transplantation.

Liver dysfunction

Liver dysfunction in patients with advanced HF is either due to congestive hepatopathy, with or without fibrosis (which may be reversible), cardiac cirrhosis (which is irreversible) or other coexisting liver disease. Abnormal liver function correlates with poorer outcomes following cardiac transplantation. Liver imaging with ultrasound lacks sensitivity for fibrosis. In selected patients, transjugular hepatic biopsy and hepatic venous pressure measurement provide additional information for risk stratification during transplant assessment.

Pre-existing neoplasm

Candidates with prior malignancy are individually evaluated in conjunction with their oncologist. Active malignancy other than localised non-melanoma skin cancer is a contraindication to transplantation. There is no arbitrary time period for observation of recurrence as this will depend on tumour type, treatment success and absence of...
metastasis. Transplantation may be considered in those with a low risk of recurrence and without evidence of metastasis.6

Multiprogn transplantation
Transplantation of heart combined with another organ (particularly heart-kidney) accounts for approximately 4% of all heart transplant volume.1 Select candidates with irreversible renal or liver dysfunction or those with fixed pulmonary hypertension may be considered for combined heart-kidney, heart-liver or heart-lung transplantation, respectively. However, the availability of organs and hence practice varies between healthcare systems and multiprogn transplantation is rare in the UK.

OUTCOMES
Outcomes following cardiac transplantation have improved considerably over the past three decades. These gains have been predominantly in the immediate post-transplant period. The 2017 ISHLT registry reports 1-year survival of approximately 85%,1 and among experienced centres this is often 90%.2 Median survival post-transplant is in the order of 12 years, and survival conditional to surviving beyond the first year, around 13–14 years.1 At our centre and others, there is now a cohort of patients surviving >30 years. Figure 1 illustrates long-term survival from the ISHLT registry.

Most patients are hospitalised for around 3 weeks after transplant, and are reviewed frequently in the first year for surveillance endomyocardial biopsies and therapeutic drug monitoring. Patients can often return to work after 3–6 months and quality of life in the majority is excellent.26

Immunosuppression
Immunosuppressive therapy is commenced at the time of transplantation and continued lifelong. Box 4 lists the most commonly used immunosuppressive medications. Most transplant centres use a combination of a calcineurin inhibitor (CNI), an antimetabolite and corticosteroid (CS) as maintenance after heart transplantation. Immunosuppression is gradually decreased after the first 3 months and about 50%–80% of patients can be weaned off CS post-transplantation.27 At 1 year, >80% are on a combination of tacrolimus and mycophenolate mofetil (MMF)/mycophenolic acid (MPA).1 The referenced reviews provide comprehensive information on drug therapies in cardiac transplantation, highlighting significant drug-drug interactions.28–30

Early post-transplant problems
Primary graft dysfunction
Primary graft dysfunction (PGD) is failure of graft function within the first 24 hours after transplantation in the absence of hyperacute rejection, pulmonary

Figure 1 Long-term survival postcardiac transplantation.1 Adult heart transplant Kaplan-Meier survival by year. NA, not available.
hypertension or known surgical complications such as bleeding or tamponade. PGD is further classified based on the affected ventricle and with specific haemodynamic and echocardiographic parameters, or the need for MCS.35 PGD is a significant problem in the immediate post-transplant period; prior to standardisation of the definition in 2014 rates between 2.3% and 28.2% were reported.31 Using the ISHLT consensus definition of PGD, rates of up to 31% have been more recently reported.32 33 In patients with severe PGD, 1-year survival of 44% has been reported in a recent series.33

Rejection
Rejection occurs as a result of interaction between the recipient immune system and the allograft. It may be categorised by the type of immune response (cell-mediated vs antibody-mediated) and by severity (ranging from mild rejection without allograft dysfunction to severe rejection with haemodynamic compromise). The incidence of rejection requiring augmentation of immunosuppression has fallen from 23.5% (2004–2006) with contemporary rates of approximately 13% (2010–2014) between discharge from hospital and 1 year.3 Surveillance endomyocardial biopsies (generally 10–12 in the first year) are performed to look for evidence of rejection. Grading is standardised according to the 2005 revised ISHLT nomenclature, which includes the use of immunohistochemistry.34

Acute cell-mediated rejection
Acute cell-mediated rejection (ACR) is uncommon after the first 12 months in patients on stable immunosuppression.35 Rates of significant ACR vary between 5% and 21%.36 Severe rejection can result in significant cardiac dysfunction, but many milder episodes are diagnosed on surveillance biopsies when patients have no or minimal symptoms and signs. Rejection is treated with augmented immunosuppression such as pulsed intravenous methylprednisolone (10 mg/kg/day for 3 days) or high-dose oral prednisolone (1 mg/kg/day tapering after 3 days), and is usually effective. Repeated episodes of ACR (grade >2R) are associated with poorer 5-year and 10-year survival.37

Antibody-mediated rejection
Antibody-mediated rejection (AMR) is thought to be caused by complement fixing anti-HLA antibodies, which may have been present pretransplant, or develop de novo post-transplant. AMR can occur early or late, and development of AMR after the first year is associated with graft dysfunction and poorer survival.38 Treatment consists of antibody removal with plasma exchange, intravenous immunoglobulin and monoclonal antibodies (eg, rituximab). The evidence base for treatment is sparse and 1-year survival following late AMR is around 50% despite therapy.39 40

Infection
The use of immunosuppression inevitably increases the risk of infection. The risk of death due to infection is greatest in the first year post-transplant.1 Immunosuppression is gradually decreased after this period. Prophylaxis is used in the first-year post-transplant against Pneumocystis jirovecii (cotrimoxazole, dapsone or pentamidine), cytomegalovirus (ganciclovir or valganciclovir), Candida (nystatin and fluconazole) and occasionally other herpes viruses (aciclovir).41 Vaccination against influenza and pneumococcal infection is recommended. Live virus vaccines are contraindicated due to the risk of disseminated infection.

Late post-transplant problems
Cardiac allograft vasculopathy
Cardiac allograft vasculopathy (CAV) is a process that leads to narrowing or occlusion of coronary arteries of the allograft. CAV affects 7.8%, 29.3% and 47.4% of patients surviving to 1, 5 and 10 years, respectively and is a significant cause of death late post-transplant.1 The mechanisms responsible for CAV are incompletely understood but are thought to be due to a combination of non-immunological and immunological insults. Risk factors for CAV are shown in box 5. The pathological lesion is a diffuse and progressive thickening of the intima due to smooth muscle proliferation, accumulation of inflammatory cells and lipid deposition that occurs in epicardial and intramyocardial vessels.42 Most patients with CAV are asymptomatic and the disease is detected on routine surveillance with grading of CAV based on angiographic features as defined by the 2010 ISHLT consensus.43 Significant CAV presents with signs and symptoms of HF, although angina can be experienced despite denervation.

Revascularisation is rarely feasible because of the diffuse nature of the disease but focal proximal lesions may be amenable to stenting. No significant difference in rates of in-stent restenosis or overall mortality has been found when comparing drug-eluting stents with bare metal stents.44 A recent meta-analysis (n=1520) examining the outcomes of coronary artery bypass surgery (CABG) versus percutaneous coronary intervention (PCI) in the
management of CAV reported a higher overall mortality (PCI 21.4% vs CAGB 42.9%) and early mortality (PCI 4.3% vs CAGB 36.4%) in the CAGB group. The use of statins post-transplant delays the onset and reduces the rate of progression of CAV. The only definitive treatment for CAV is retransplantation; however, very few patients are eligible for this given the donor organ shortage. Mammalian target of rapamycin inhibitors (mTORi) may delay onset and slow progression of CAV, but may be effective only when introduced early post-transplant. In addition to CAV, chronic immune injury also results in fibrosis and diastolic dysfunction.

Malignancy

There is geographical variation in the incidence and type of malignancy following cardiac transplantation with a 10.7% risk of any de novo solid organ malignancy between 1 and 5 years post-transplant. Many of the common tumours are driven by viral infection including human papilloma virus (HPV), Epstein-Barr virus (EBV) and human herpes virus 8 (HHV8). Squamous cell carcinoma of the skin (HPV driven) is the most common malignancy reported in around 10% of 5-year survivors and 18% of 10-year survivors. Multiple and recurrent tumours are often found, particularly in patients with sun-damaged skin. Sun avoidance is therefore recommended. Non-lymphoma malignancy is the leading cause of death late after transplant, accounting for approximately 20% of deaths in those surviving >5 years.

Post-transplant lymphoproliferative disease (PTLD) is driven by latent EBV present in lymphocytes, is usually a non-Hodgkin's B-cell tumour, and has a bimodal distribution in time of presentation with the first peak in the first year after transplant. The incidence of PTLD in the cardiac transplant recipients has previously been reported between 3%–9%. It can regress if immunosuppression is significantly reduced, but chemotherapy is required in many cases. The 5-year survival rate following first diagnosis of PTLD is around 20%. Kaposi’s sarcoma (HHV8 related) is uncommon in the UK and more frequently encountered in Central African, Mediterranean and Middle Eastern patients.

Renal dysfunction

Within the first year following transplantation, 8.6% of recipients have either serum creatinine >221 μmol/L, or require renal replacement therapy (chronic dialysis or renal transplant). The development of chronic renal dysfunction (glomerular filtration rate ≤29 mL/min/1.73 m² body surface area(BSA)) following transplantation is associated with a fourfold increase risk of death. CNIs and poorly treated hypertension are associated with the development of renal dysfunction. Acute CNI toxicity is due to afferent renal arterial vasoconstriction and is reversible. Late renal dysfunction is related to tubular damage and tends to be progressive, even when CNI is discontinued. The use of CNI-free regimes with mTORIs offers a sustained renal advantage, but these are associated with higher rates of biopsy-proven acute rejection and drug-related adverse events. Selected heart recipients who have developed renal failure but maintained good cardiac allograft function can be considered for renal transplantation. The ISHLT registry reports renal transplant in 3.8% of those alive at 10 years.

Hypertension

Antihypertensive therapy is required in up to 70% of patients post-transplantation. The incidence is higher in male recipients treated with ciclosporin. Dihydroyridine calcium channel antagonists and ACE inhibitors are commonly used as treatment. Hypertension also contributes to development of renal dysfunction and CAV.

Hyperlipidaemia

Elevated lipids in heart transplant recipients may be due to pre-existing dyslipidaemia or secondary to immunosuppression. Early use (predischARGE) of pravastatin after transplantation is associated with improved 1-year survival, reduced incidence of rejection with haemodynamic compromise and CAV. This is due to both the immune-modulating and lipid-lowering effects of statins. Current practice is to commence a statin after transplant regardless of lipid levels.

Diabetes

Cumulative incidence of diabetes mellitus (DM) in heart transplant recipients is approximately 35% at 5 years. Use of CS and CNIs (tacrolimus >ciclosporin) for immunosuppression can be contributory. Post-transplant DM is associated with a greater incidence of post-transplant hypertension and renal dysfunction with no difference in overall survival. The 2003 international consensus guidelines provide further details on its management.

Pregnancy after cardiac transplantation

Pregnancy following cardiac transplantation should ideally be planned and is discouraged in the first year. All recipients should be counselled regarding risks of pregnancy and contraceptive choices. Barrier methods of contraception are inadequate and may only be recommended as an adjunct. Monitoring of immunosuppression levels is required when starting the combined contraceptive pill/oral contraceptives due to inhibition of the CYP-4503A4 pathway. The Mirena intrauterine device can be used in uncomplicated transplant recipients. Pregnant recipients require specialist care under a multidisciplinary team including the high-risk pregnancy service. In the female recipient, CNIs and CS may be continued throughout pregnancy with discontinuation of MMF/MPA at least 6 weeks preconception. Male recipients are advised to discontinue MMF/MPA before fathering children due to the risk of teratogenicity. The required dose of CNIs to maintain...
therapeutic levels increases markedly in the second trimester, however with frequent monitoring of drug levels pregnancy can be managed safely. Importantly, preconception counseling should highlight the limited longevity of the graft and the potential risk of an inherited cardiac condition. There is an increased risk of small-for-date babies and hypertensive disorders of pregnancy but major teratogenic effects are uncommon if appropriate precautions are taken.

**FUTURE PERSPECTIVES**

**Increasing potential organs for transplantation**

Traditionally, cardiac allografts have been obtained as a result of donation after brainstem-determined death (DBD). Since 2015, centres in Australia and the UK have used hearts that have been obtained as a result of donation after circulatory-determined death (DCD). In the world’s largest cohort of DCD heart transplantation, allograft performance and 1-year survival is similar to DBD heart transplantation, although medium-term and long-term outcome data are not yet available. Ex vivo machine perfusion of donor hearts may allow the use of organs previously considered unsuitable. There is the potential to significantly increase the number of available hearts for transplantation with increasing experience and use of these techniques.

**Reducing complications to improve survival**

Improving the detection of rejection and reducing the number of invasive biopsies required has attracted considerable research attention. In a select recipient population at low risk for rejection, gene expression profiling of peripheral blood has reduced biopsy numbers without an increased risk of serious adverse outcomes. This has not yet been validated in the diagnosis of AMR. The detection and measurement of donor-derived cell-free DNA using targeted quantitative genotyping is another development in the evolving field of non-invasive detection of rejection.

**CONCLUSION**

The milestone 50th year of cardiac transplantation marks a time for reflection and celebration of the progress made since the first operation of its kind in 1967. Key to the success of heart transplantation is appropriate candidate selection, as while survival (predominantly early survival) has improved, the limited donor pool along and long-term morbidity and graft longevity limits transplantation as a treatment rather than a cure for HF. Underpinning every transplant performed is the generosity of donors and their families. It is the fiduciary duty of all involved in this field to maximise the potential benefit from each organ donated as the developments of the future aim to increase graft longevity and recipient quality of life.

**Supplementary file 1**

**REFERENCES**


49 Kobashigawa JA, Itagaki BK, Razi RR, et al. Correlation between myocardial fibrosis and restrictive cardiac physiology...