Table 1: Baseline characteristics

	Occult renal impairment (n = 503)		Normal (n = 1339)		P-value
Age (years)	73.6 ± 6.4		64.1 ± 9.1		<0.01
≥75	240	48%	149	11%	<0.01
Male gender	327	65%	1057	79%	<0.01
Estimated glomerular filtration rate (ml/min/1.73 m^2)	51.3 ± 6.6		85.8 ± 23.0		<0.01
Body mass index	21.6 ± 2.8		24.5 ± 3.0		<0.01
Emergency procedure	38	8%	62	5%	0.01
Old myocardial infarction	210	42%	388	29%	<0.01
Heart failure	124	25%	240	18%	<0.01
Ejection fraction (%)	59.6 ± 14.8		61.6 ± 13.5		<0.01
Stroke history	119	24%	236	18%	<0.01
Peripheral arterial disease	118	23%	213	16%	<0.01
Atrial fibrillation	24	5%	62	5%	0.89
Chronic obstructive pulmonary disease	16	3%	21	2%	0.03
Hypertension	346	69%	967	72%	0.67
Diabetes mellitus	215	43%	581	43%	0.83
Hyperlipidaemia	235	47%	761	57%	<0.01
Anaemia (haemoglobin <12 mg/dl)	203	40%	255	19%	<0.01
Current smoker	88	17%	380	28%	<0.01
Malignancy	42	8%	74	6%	0.03
Coronary characteristics					
Triple-vessel disease	358	71%	853	64%	<0.01
Left main disease	141	28%	401	30%	0.42
Chronic total occlusion	212	42%	603	45%	0.27
Proximal left anterior descending artery disease	300	60%	793	59%	0.87

coronary intervention (PCI) or CABG and excludes those with acute myocardial infarction within a week before the index procedure [12]. This study was approved by the institutional review boards or ethics committees of all participating institutions (see Supplemental Table). Because the subjects were retrospectively enrolled, written informed consent was not obtained, in accordance with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan. Seventy-three patients were excluded because of their refusal to participate in the study when contacted for follow-up [12].

Between January 2000 and December 2002, 9877 patients were identified as having undergone either PCI (6878 patients) or CABG (2999 patients) without a prior history of coronary revascularization. Among the 2999 patients undergoing CABG, 484 undergoing concomitant valvular, left ventricular or major vascular operations were excluded from the current analysis. Among the 2515 patients undergoing isolated CABG, those with normal SCr levels (0.6–1.1 mg/dl for males; 0.4–0.8 mg/dl for females) were included. Therefore, the study group comprised 1842 patients with normal SCr who were undergoing their first isolated CABG.

Data collection and definitions

Demographic, angiographic and procedural data were collected from hospital charts or databases at the various centres by independent clinical research coordinators according to pre-specified definitions. Baseline clinical characteristics, such as myocardial infarction, heart failure, diabetes, hypertension, current smoker status, atrial fibrillation, chronic obstructive lung disease and malignancy, were regarded as present when these diagnoses were recorded in the hospital charts. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or echocardiography. Anaemia was defined as a blood haemoglobin level of <12 g/dl, as previously described [12].

Estimated GFR (eGFR, ml/min/1.73 m^2) was estimated by the Cockcroft–Gault formula [13, 14]. Renal impairment was regarded as present when GFR estimated by the Cockcroft–Gault formula was less than 60 ml/min/1.73 m^2, as per the National Kidney Foundation's definition [15]. Thus, ORI was defined as an impaired eGFR (<60 ml/min/1.73 m^2) with a normal SCr level.

End-points

An independent clinical events committee adjudicated events. Death was regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified. Any death during the index hospitalization was regarded as cardiovascular death. Myocardial infarction was adjudicated according to the definition in the Arterial Revascularization Therapy Study [16]. Within 1 week of the index procedure, only Q-wave myocardial infarction was adjudicated as myocardial infarction. Stroke was defined as any new permanent global or focal neurological deficit that could not be attributed to other neurological or medical processes. In the majority of patients, strokes were diagnosed by neurologists and confirmed by computed tomography or magnetic resonance imaging head scans. Stroke at follow-up was defined as symptomatic stroke.

The primary end-point measure was death from any cause. Secondary end-points were stroke, myocardial infarction, the need for any revascularization procedures and major adverse cardiovascular events (MACEs; which include death, stroke or myocardial infarction) during the follow-up period. As in-hospital end-points, the need for postoperative dialysis and the ratio of peak postoperative to preoperative Cr ≥2 were also evaluated.

Table 2: CABG data

	Occult renal impairment (n = 503)	Normal (n = 1339)	P-value
Off-pump	54.3%	56.3%	0.43
No. of anastomotic sites	3.3 ± 1.2	3.3 ± 1.1	0.57
Type of bypass grafts			
Left internal thoracic artery	90.7%	94.4%	<0.01
Right internal thoracic artery	29.0%	31.4%	0.33
Right gastroepiploic artery	21.5%	29.1%	<0.01
Radial artery	28.0%	39.1%	<0.01
Saphenous vein	67.6%	53.6%	<0.01

Statistical analyses

All continuous variables were expressed as the mean ± standard deviation. Differences in baseline characteristics between the two groups were examined by an unpaired t-test and a Fisher's exact test. Categorical variables were presented as number and percentage and were compared with a χ^2 test. Cumulative incidence was estimated by the Kaplan–Meier method, and differences were assessed using a log-rank test. Outcomes after CABG in the presence or absence of ORI were compared by logistic regression or Cox proportional hazards models. Cox proportional hazards models were adjusted for the following clinically relevant confounders: age, gender, body mass index, emergency procedure, prior myocardial infarction, congestive heart failure, stroke, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, hypertension, diabetes mellitus, hyperlipidaemia, anaemia, current smoker status, on- or off-pump surgery, triple-vessel disease, left main disease, total occlusion, proximal left anterior descending artery disease and use of left internal thoracic artery, right internal thoracic artery, gastroepiploic artery, radial artery or saphenous vein. They were consistent with previous reports from the current registry. Continuous variables were dichotomized using clinically meaningful reference values or median values.

All reported P-values were two-sided. All analyses were conducted by a statistician using SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA) and S-Plus version 7.0 (Insightful, Corp., Seattle, WA, USA). The authors had full access to the data and take responsibility for its integrity.

RESULTS

Baseline characteristics and operative outcomes

Of the 1842 patients undergoing CABG with normal SCr levels, 503 (27.3%) had ORI. The baseline characteristics of the patients in the two groups are presented in Table 1. The ORI group included more elderly patients, but fewer male and lower body mass index patients. In addition, the ORI group generally included patients with heart failure, history of stroke and peripheral arterial disease. Preoperative coronary characteristics were similar between the groups, except for the ratio of triple-vessel disease. The ratio of off-pump surgery and the average number of anastomotic sites per patient were similar between the groups (Table 2). Arterial grafts in such vessels as the left internal thoracic artery, the gastroepiploic artery and the radial artery were used more commonly in the Normal group.

Table 3: Observed in-hospital outcomes

	Occult renal impairment (n = 503)		Normal (n = 1339)		P-value
Death	16	3.2%	13	1.0%	<0.01
Stroke	12	2.4%	16	1.2%	0.06
Myocardial infarction	11	2.2%	16	1.2%	0.11
Need for dialysis	10	2.0%	3	0.2%	<0.01
Post/pre Cre ≥2[a]	47	9.3%	82	6.1%	0.02

[a]Ratio of peak postoperative to preoperative SCr level.

Table 4: Adjusted in-hospital outcomes (occult renal impairment vs normal)

	Hazard ratio	95% CI		P-value
Death	2.41	1.04	5.57	0.04
Stroke	1.76	0.81	3.85	0.15
Myocardial infarction	1.76	0.81	3.84	0.15
Need for dialysis	5.93	1.46	24.12	0.01
Post/pre Cre ≥2[a]	1.33	0.87	2.02	0.19

[a]Ratio of peak postoperative to preoperative SCr level.

In-hospital outcomes

Observed in-hospital mortality was significantly higher in the ORI group (3.2 vs 1.0%, P < 0.01; Table 3). In-hospital incidence of stroke in the ORI group tended to be higher than the Normal group (P = 0.06). The need for dialysis after CABG was more common in the ORI group (2.0 vs 0.2%, P < 0.01). In addition, patients with a ratio of post- to preoperative SCr level of ≥2 were more common in the ORI group (9.3 vs 6.1%, P = 0.02). A similar tendency was seen in the adjusted outcomes (Table 4). Adjusted in-hospital mortality was also significantly higher in the ORI group (odds ratio [95% confidence interval]: 2.41 [1.04–5.57], P = 0.04). The need for dialysis after CABG was more common in the ORI group (5.93 [1.46–24.12], P = 0.01).

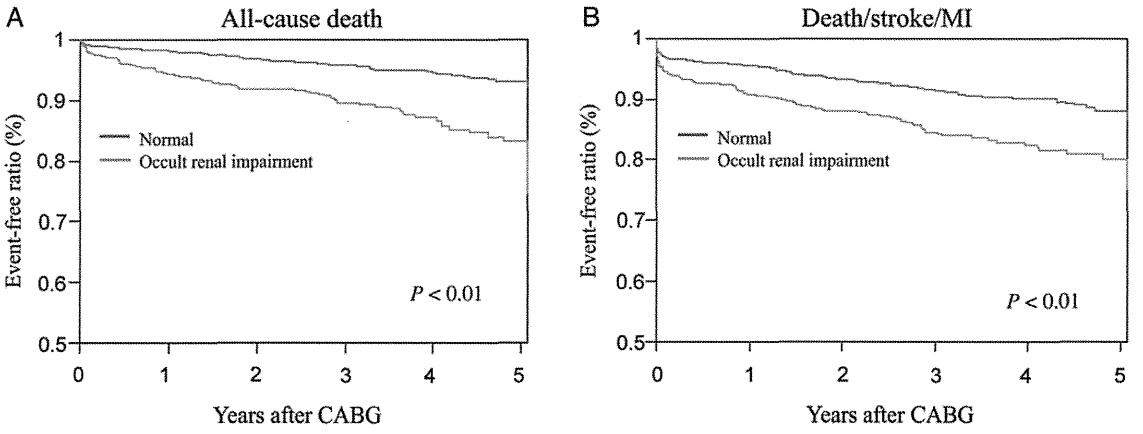

Figure 1: Kaplan–Meier curves for all-cause death and major adverse cardiovascular events in the presence or absence of occult renal impairment. (**A**) All-cause death. (**B**) Major adverse cardiovascular event (death, stroke or myocardial infarction [MI])

Table 5: Hazard ratios for late outcomes after CABG in patients with vs without occult renal impairment

	Event (%)				Occult renal failure vs Normal			
	Occult renal impairment (n = 503)		Normal (n = 1339)		Hazard ratio	95% CI		P-value
Death	67	13.3%	71	5.3%	1.72	1.16	2.54	<0.01
Stroke	43	8.5%	73	5.5%	1.45	0.96	2.18	0.08
Myocardial infarction	19	3.8%	37	2.8%	1.38	0.79	2.40	0.26
Any revascularization	59	11.7%	171	12.8%	0.96	0.71	1.30	0.81
MACE[a]	108	21.5%	155	11.6%	1.53	1.16	2.02	<0.01

[a]Composite of death, stroke or myocardial infarction.

Long-term outcomes

Clinical follow-ups were completed for 98% of cases at 1 year and for 95% of cases at 2 years. The median follow-up period was 3.7 years. Figure 1 shows the Kaplan–Meier curves for survival and freedom from MACEs after CABG. Cumulative survival in the ORI and the Normal groups were 94.4 and 98.1% at 1 year and 83.2 and 93.1% at 5 years, respectively (P < 0.01). Similarly, freedom from MACEs was higher in the Normal group (P < 0.01).

Adjusted all-cause mortality was significantly higher in the ORI group (1.72 [1.16–2.54], P < 0.01, Table 5). Adjusted incidence of stroke, myocardial infarction and need for any revascularization did not differ between the groups. However, the incidence of MACEs was significantly higher in the ORI group (1.53 [1.16–2.02], P < 0.01).

DISCUSSION

Principal findings

Preoperative renal impairment is considered an independent risk factor for mortality and morbidity after CABG [1–4]. SCr is the most popular test for renal impairment. However, some populations had impaired renal function despite normal SCr levels. In the present study, we sought to investigate the impact of ORI on early and late outcomes after CABG. To the best of our knowledge, this is the first report to investigate the late outcome of ORI patients. In addition, there has been no multicentre registry that has investigated the impact of ORI after CABG.

Observed in-hospital outcomes revealed that ORI was associated with high mortality compared with normal renal function. In addition, patients with ORI were associated with a higher need for postoperative dialysis and a higher peak postoperative SCr level. Adjusted in-hospital outcomes also revealed that patients with ORI were associated with higher mortality and the need for dialysis after CABG. In terms of late outcomes, patients with ORI were associated with poor survival compared with those with normal renal function. In addition, ORI was associated with a high incidence of major cardiovascular events. These outcomes indicate that routine estimation or measurement of GFR should be preferred over SCr as a screening method for the detection of higher-risk patients undergoing CABG. This study is important because we demonstrated that ORI is an independent risk factor of death after CABG not only for the in-hospital period but also for the long term.

The relationship between preoperative renal function and postoperative outcomes has been reported in a number of studies [1–4]. SCr level measurement is easy and is the most popular method used to evaluate preoperative renal function in screening tests. However, its use has been questioned in several studies, because it can be normal in spite of impaired renal function and it may underestimate mild renal dysfunction [5–8]. A more accurate approximation of renal function can be obtained using

the Cockroft-Gault equation to calculate an eGFR from SCr. Several studies have reported the greater accuracy of eGFR compared with SCr in estimating the prognosis after cardiac surgery [10, 11, 17–19].

Renal dysfunction is an adverse prognostic factor in patients with coronary artery disease [20]. In patients undergoing CABG, moderate and end-stage renal dysfunction are recognized risk factors for increased perioperative mortality and are accounted for in the commonly used cardiac risk stratification scoring systems [21, 22]. In addition, severe preoperative renal disease is associated with a higher incidence of morbidity, need for dialysis and longer hospital stay after CABG [23]. However, limited information exists regarding the influence of normal renal function on the immediate postoperative mortality and long-term survival of patients undergoing isolated first-time CABG.

Several reports have investigated the outcomes of normal renal function to mild renal dysfunction after cardiac surgery. Wijeysundera *et al.* [19] reported that among 10 751 patients with normal SCr levels undergoing cardiac surgery using cardiopulmonary bypass, 13% had ORI. Compared with patients with normal renal function, those with ORI experienced a more-than threefold an increased risk of in-hospital mortality and renal replacement therapy after cardiac surgery. Wang *et al.* [10] reported that among 4603 patients with normal plasma Cr levels undergoing cardiac surgery, 12.3% had ORI and that ORI was associated with an increased risk of in-hospital mortality, renal failure requiring dialysis and major morbidity, such as cardiovascular, respiratory, neurological, renal dysfunction and infection. In addition, estimated Cr clearance remained a significant predictor of these outcomes, but plasma Cr level was not a predictor of any outcomes.

Specifically for CABG, Noyez *et al.* [11] compared the risk stratification by level of SCr with estimated C clearance in 627 patients undergoing isolated CABG. They concluded that the association between preoperative renal failure and adverse outcomes after CABG is stronger with the estimated Cr clearance than with the routinely used SCr and that routine estimation or measurement of Cr clearance should be preferred over SCr as a screening method for the detection of higher-risk patients undergoing CABG. A large single-centre registry of 9159 patients with normal SCr undergoing CABG by Miceli *et al.* [17] reported that ORI was associated with a doubling in the risk of operative mortality, postoperative renal dysfunction and need for dialysis. In addition, ORI increased the risk of stroke, arrhythmia and prolonged hospital stay. However, all of these reports were limited to early outcomes.

There are several important limitations to this study. First and most importantly, observational studies have problems related to biases and unmeasured confounders. Multivariate analyses may not adequately adjust for these biases. Second, we used the Cockcroft-Gault equation to estimate GFR because it has been most generally used in clinical settings. However, we should have used another method to calculate GFR. GFR can be calculated based on SCr (the Cockcroft-Gault, the Modification of Diet in Renal Disease [MDRD] study or Chronic kidney disease Epidemiology Collaboration [CKD-EPI] equations) or on Cystatin C [24, 25]. Using SCr has significant disadvantages, such as the inability to measure renal function correctly when impairment is 50% or less. Creatinine generation is proportional to muscle mass and related to an individual's age, sex, race and weight. On the other hand, Cystatin C is a cysteine protease inhibitor with a molecular mass of 13 kDa. It has been shown that cystatin C is a more sensitive marker of GFR changes than SCr because its levels are not affected by muscle mass, age, inflammation, fever or exogenous agents. Finally, we have adjusted the differences of patients' backgrounds (e.g. age, sex, myocardial infarction, heart failure) using propensity score analysis. However, the analysis may not adequately adjust for these biases. In addition, our study was non-randomized; potential confounders may influence our outcomes.

CONCLUSIONS

ORI is an independent risk factor of early and late death as well as MACEs in patients undergoing CABG with normal SCr levels. A more accurate evaluation of renal function through a combination of SCr and eGFR may facilitate a better risk stratification that can optimize therapeutic strategies.

SUPPLEMENTARY DATA

Supplementary material is available at *ICVTS* online.

Funding

This work was supported in part by a Grant for Clinical Research for Evidence Based Medicine from the Ministry of Health, Labor and Welfare in Japan to T. Kimura and an educational grant from the Research Institute for Production Development (Kyoto, Japan).

Conflict of interest: none declared.

REFERENCES

[1] Cooper WA, O'Brien SM, Thourani VH, Guyton RA, Bridges CR, Szczech LA *et al.* Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the society of thoracic surgeons national adult cardiac database. Circulation. 2006;113:1063–70.

[2] Chikwe J, Castillo JG, Rahmanian PB, Akujuo A, Adams DH, Filsoufi F. The impact of moderate-to-end-stage renal failure on outcomes after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2010;24:574–9.

[3] Charytan DM, Yang SS, McGurk S, Rawn J. Long and short-term outcomes following coronary artery bypass grafting in patients with and without chronic kidney disease. Nephrol Dial Transplant 2010;25:3654–63.

[4] Zakeri R, Freemantle N, Barnett V, Lipkin GW, Bonser RS, Graham TR *et al.* Relation between mild renal dysfunction and outcomes after coronary artery bypass grafting. Circulation 2005;112:I270–5.

[5] Kellen M, Aronson S, Roizen MF, Barnard J, Thisted RA. Predictive and diagnostic-tests of renal failure: a review. Anesth Analg 1994;78:134–42.

[6] Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. New Engl J Med 2006; 354:2473–83.

[7] Duncan L, Heathcote J, Djurdjev O, Levin A. Screening for renal disease using serum creatinine: who are we missing? Nephrol Dial Transpl 2001; 16:1042–6.

[8] Swedko P, Clark HD, Paramsothy K, Akbari A. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med 2003;163:356–60.

[9] Rashid ST, Salman M, Agarwal S, Hamilton G. Occult renal impairment is common in patients with peripheral vascular disease and normal serum creatinine. Eur J Vasc Endovasc 2006;32:294–9.

[10] Wang F, Dupuis JY, Nathan H, Williams K. An analysis of the association between preoperative renal dysfunction and outcome in cardiac surgery—estimated creatinine clearance or plasma creatinine level as measures of renal function. Chest 2003;124:1852–62.

[11] Noyez L, Plesiewicz I, Verheugt FWA. Estimated creatinine clearance instead of plasma creatinine level as prognostic test for postoperative renal function in patients undergoing coronary artery bypass surgery. Eur J Cardiothorac Surg 2006;29:461–5.

[12] Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Shizuta S, Ehara N *et al.* Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. Circulation 2008;118:S199–209.
[13] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[14] Gault MH, Longerich LL, Harnett JD, Wesolowski C. Predicting glomerular function from adjusted serum creatinine. Nephron 1992;62:249–56.
[15] Patel SS, Kimmel PL, Singh A. New clinical practice guidelines for chronic kidney disease: a framework for K/DOQI. Semin Nephrol 2002; 22:449–58.
[16] Serruys PW, Ong ATL, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJRM *et al.* Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease—the final analysis of the arterial revascularization therapies study (ARTS) randomized trial. J Am Coll Cardiol 2005; 46:575–81.
[17] Miceli A, Bruno VD, Capoun R, Romeo F, Angelini GD, Caputo M. Occult renal dysfunction: a mortality and morbidity risk factor in coronary artery bypass grafting surgery. J Thorac Cardiovasc Surg 2011;141:771–6.
[18] Najafi M, Goodarzynejad H, Karimi A, Ghiasi A, Soltaninia H, Marzban M *et al.* Is preoperative serum creatinine a reliable indicator of outcome in patients undergoing coronary artery bypass surgery? J Thorac Cardiovasc Surg 2009;137:304–8.
[19] Wijeysundera DN, Karkouti K, Beattie WS, Rao V, Ivanov J. Improving the identification of patients at risk of postoperative renal failure after cardiac surgery. Anesthesiology 2006;104:65–72.
[20] Best P. Cardiovascular disease and chronic kidney disease: insights and an update. Am Heart J 2004;148:230–42.
[21] Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;24:881–2.
[22] Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB *et al.* The society of thoracic surgeons 2008 cardiac surgery risk models: part 1–coronary artery bypass grafting surgery. Ann Thorac Surg 2009;88:S2–2.
[23] Parikh DS, Swaminathan M, Archer LE, Inrig JK, Szczech LA, Shaw AD *et al.* Perioperative outcomes among patients with end-stage renal disease following coronary artery bypass surgery in the USA. Nephrol Dial Transplant 2010;25:2275–83.
[24] Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Ann Intern Med 2012;156:785–95, W-270, W-271, W-272, W-273, W-274, W-275, W-276, W-277, W-278.
[25] Feng JF, Qiu L, Zhang L, Li XM, Yang YW, Zeng P *et al.* Multicenter study of creatinine- and/or cystatin c-based equations for estimation of glomerular filtration rates in chinese patients with chronic kidney disease. PLoS One 2013;8:e57240.

eComment. Renal dysfunction may predict early and late cardiovascular events

Authors: ***Sevket Balta, Sait Demirkol, Murat Unlu and Zekeriya Arslan***
Department of Cardiology, Gulhane Medical Faculty, Ankara, Turkey
doi: 10.1093/icvts/ivt344

We read with interest the article 'Impact of occult renal impairment on early and late outcomes following coronary artery bypass grafting' by Marui *et al.* [1]. They concluded that occult renal impairment was an independent risk factor for early and late death as well as cardiovascular events in patients undergoing CABG with normal creatinine levels. CABG is closely related to renal dysfunction. Serum creatinine level is the most common test for renal failure. The glomerular filtration rate (GFR) provides more sensitive information about renal function than the serum creatinine level. The GFR can be measured by the formula of modification of diet in renal disease (MDRD) and the Cockcroft-Gault equation. GFR was estimated using the simplified Cockcroft-Gault equation in the current study [1]. However, the Cockcroft-Gault equation may estimate lower GFR in younger age groups compared with the MDRD formula, but it can measure higher GFR in older individuals compared with the MDRD formula [2]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recently published an equation for GFR using the same variables (serum creatinine level, age, sex and race) as the MDRD formula. However, the CKD-EPI equation more precisely categorized individuals with respect to long-term clinical risk of incident end-stage renal disease, all-cause mortality, coronary heart disease and stroke compared with the MDRD formula [3]. In conclusion, renal dysfunction is an important factor in predicting early and late outcomes following CABG. Novel methods for measurement of GFR in patients having CABG will enlighten future studies.

Conflict of interest: none declared

References

[1] Marui A, Okabayashi H, Komiya T, Tanaka S, Furukawa Y, Kita T *et al.* Impact of occult renal impairment on early and late outcomes following coronary artery bypass grafting. Interact CardioVasc Thorac Surg 2013;17:638–43.
[2] Balta S, Demirkol S, Karaman M. Renal dysfunction may predict new onset heart failure. Am Heart J 2013; doi:10.1016/j.ahj.2013.06.005.
[3] Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis 2010;55:648–59.

Mini Review

Strategies in cell therapy for cardiac regeneration

Hidetoshi Masumoto[1, 2] and Jun K. Yamashita[1, 3, *]

[1)]Department of Cell Growth and Differentiation, Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan
[2)]Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan
[3)]Department of Stem Cell Differentiation, Institute for Frontier Medical Sciences, Kyoto University, Kyoto, Japan

Cardiac regenerative medicine is emerging as a new approach to treat severe cardiovascular diseases that are resistant to conventional therapies. To achieve fair engraftment and efficient outcome, the method of cell transplantation is important, as the efficacy of engraftment after simple needle injection is relatively poor. Using biomaterials (e.g. collagen, fibrin, gelatin or matrigel) as a scaffold of the transplanted cells is an effective method, and various attempts to control cell distribution for the creation of tissue-like structure have been made. In this regard, scaffold-free cell sheet technology using temperature-responsive culture surface is another promising method because it bears potential for generating three-dimensional tissue-like structure *in vitro*. Furthermore, the cell sheet system enables us to elucidate the cellular mechanisms for cardiac regeneration. Combination of cell therapy and sustained release of growth factors, such as basic fibroblast growth factor, is another valuable approach for cell engraftment and augmentation of the potential of cell transplantation. Herein, we review various engraftment strategies of the transplanted cells to achieve more efficient outcome in cardiac cell therapy. We expect that these advanced modalities with bioengineering technology would largely contribute to cardiac regenerative medicine.

Rec.8/16/2012, Acc.10/3/2012, pp114-120

*Correspondence should be addressed to:
Jun K Yamashita, MD, PhD, Department of Stem Cell Differentiation, Institute for Frontier Medical Sciences, Kyoto University, 53 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. Phone: +81-75-751-3853, Fax: +81-75-751-4824, E-mail: juny@frontier.kyoto-u.ac.jp

Key words biomaterials, cardiac cell therapy, cardiac regeneration, cell sheet

Introduction

Cardiovascular disease remains the leading cause of death worldwide. A boundary for conventional severe heart failure treatments exists in Japan due to the shortage of heart donors[1)]. This health problem has prompted research into new therapeutic approaches including cardiac regeneration[2)].

With the discovery of various stem cell populations possessing cardiogenic potential, and the subsequent ability to isolate and expand these cells, the notion of a restor-

ative therapy using stem cells has begun to take shape. Acute ischemic injury and chronic cardiomyopathies lead to permanent loss of cardiac tissue and following heart failure. For these pathologic conditions, cell transplantation is thought to be an ideal therapeutic method for replacing the lost myocardium[3,4], and stem cell research and clinical trials for cardiac cell therapy are now being prioritized[2,5].

In spite of the substantial knowledge gained through numerous basic research studies, significant barriers to true cardiac regeneration remain, and the field still lacks sufficiently conclusive results to support full-scale implementation of such therapies. A major reason for the inadequate results would be the poor engraftment of the transplanted cells. Results from these researches have reached the conclusion that stem cells may be beneficial in the treated hearts but act primarily through paracrine mechanisms, including angiogenesis, apoptosis prevention and promotion of healing, rather than through direct differentiation as initially expected[2]. The low level of grafted cell survival and engraftment diminishes their potential, and is a potent technical limitation for stem cell therapy[6]. It is reported that more than 70% of the cells die during the first 48 hours after needle injection, being progressively lost during the following days due to the hypoxic, inflammatory, and/or fibrotic environment[7]. Another report indicates that only 5.4 to 8.8% of microspheres directly injected into the beating myocardium remain just after the injection due to massive mechanical loss[8]. Thus, new strategies like combination of the cells with bioengineering techniques have been developed and are being subjected to intense research, suggesting that new strategies may improve the efficiency of stem cell therapies. In this review, we introduce transplantation technologies for effective engraftment of the transplants and attempts to increase the efficacy of cell transplantation. The approaches reviewed here are summarized in Table 1.

Table 1 Approaches to improve engraftment of transplanted cells

	References
● Scaffolding with biomaterials	
Cell injection with collagen / fibrin / gelatin / Matrigel	9)
Cellular patches using biomaterials	11), 13)
3D contractile cardiomyocyte-loops using collagen	12)
Organized construct as parallel channels	14)
● Scaffold-free approaches	
Cardiac tissue patches	15)
Cell sheets Temperature-responsive culture dishes Fibrin polymer coated culture dishes Magnetic force-based cell sheets	 16), 17), 18) 19) 20)
3D cardiosphere	24)
● Combinatory approaches with cell transplantation	
Sustained release of cytokines (bFGF etc.)	21), 22), 23)
Pericardium wrapping	25)
Omental wrapping	26), 27), 28)

3D: three-dimensional, bFGF: basic fibroblast growth factor

Biomaterials scaffolding the transplanted cells

Initial experiments were performed by combining the cells with injectable biomaterials such as collagen, fibrin, or gelatin. Matrigel or other factors providing a favorable environment rich in cytokines and growth factors were also tested. In general, these early studies showed an increased survival of the transplanted cells and a greater improvement of the cardiac function of the transplanted hearts[9]. However, these approaches did not assure complete cell retention or an adequate distribution of the grafted cells. Techniques, like the creation of cell sheets or patches as microtissues, are now being developed in order to allow, together with a greater cell survival, a more homogeneous and organized distribution of the cells[10].

The creation of cellular patches has been developed by using biomaterials which act as a delivery platform for the cells, assuring their engraftment and interaction with the tissue. With hydrogel/extracellular matrix (ECM)-based matrices, the cells are usually embedded in soluble hydrogels matrices that can condensate after temperature changes, forming a cellularized patch that can be applied to the heart pericardium. The creation of a patch with mesenchymal stem cells (MSCs) entrapped in a collagen-I matrix was reported, and the application to rat infarcted hearts induced an increase of cell engraftment and a functional improvement, due to the trophic effect of the MSC potentiated by increasing their survival in the tissue[11]. Three-dimensional (3D) contractile loops of mixed collagen and neonatal cardiomyocytes, a more-sophisticated approach, have been successfully created. Implantation of these loops could support the contractile function of the damaged heart[12]. On the other hand, porous biomaterials,

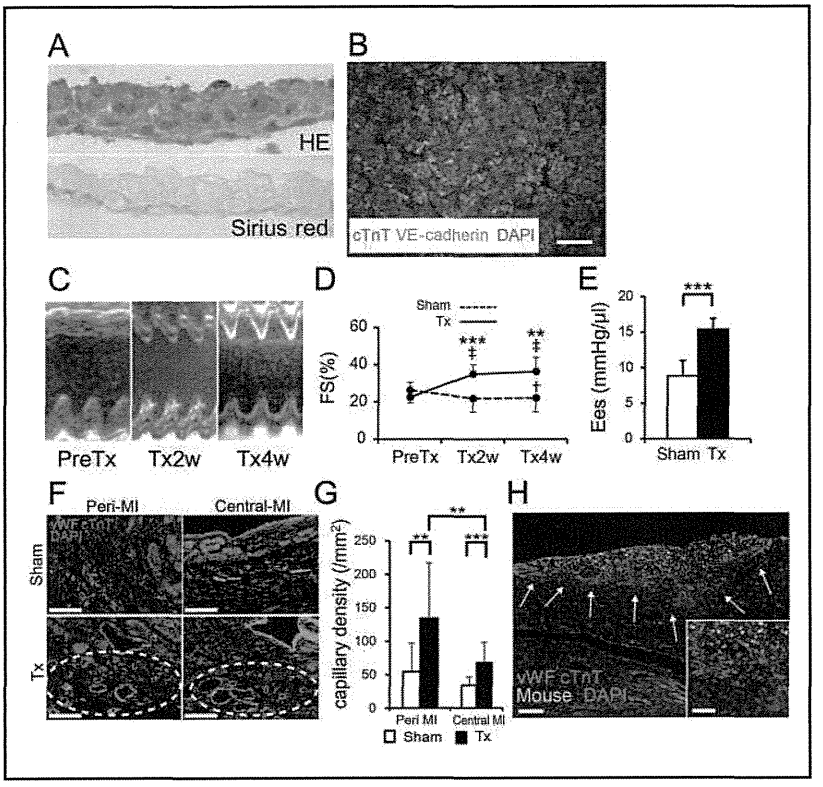

Fig.1 The improvement of infarcted heart function after transplantation of cardiac tissue sheets bioengineered with mouse ES cell-derived defined cardiac cell populations

(A): Cross-sections of the sheet. Upper panel: H&E staining showing cell appearance of the sheet. Lower panel: Sirius red staining showing intact extracellular matrix. (B): Immunostaining of sheets for cTnT (red), VE-cadherin (green), and DAPI. (C,D): Echocardiogram (n=9). (C): Representative M-mode image. Note that infarct anterior wall started to move 2-4 weeks after transplantation (Tx). (D): Fractional shortening (FS). (E): LV pressure-volume loop study 4 weeks after Tx (n=8). Ees: End-systolic elastance. (F,G): Capillary formation at Tx-d28. (F): Double staining for vWF (ECs, green) and cTnT (cardiomyocytes [CMs], red) at peri-MI and central-MI areas. Note that newly formed capillaries are clearly observed in transplantation group (dotted circles). (G): Quantification of capillary density (capillary number per square millimeter). Peri-MI area (left panel) and central-MI area (right panel) (15 views each). (H): Triple staining for vWF, cTnT, and species-specific fluorescent in situ hybridization (mouse nuclei, yellow) (Tx-d3). Most of the accumulated vWF-positive cells are negative for mouse nuclear staining (arrows). Inset: higher magnification view.

$^{**}p < 0.01$; and $^{***}p < 0.001$ (unpaired *t* test), $^{\dagger}p < 0.05$ and $^{\ddagger}p < 0.01$ (vs. PreTx, paired t test). PreTx; Pretransplantation, Tx2w, Tx4w; 2 and 4 weeks after transplantation, respectively. Scale bars: 200 μm in (B), 100 μm in (F) and (H) (main panel), 50 μm in (H) (inset). HE, Hematoxylin and Eosin; cTnT, cardiac troponin-T; DAPI, 4,6-diamidino-2-phenylindole; vWF, von Willebrandfactor; MI, myocardial infarction. (quote from ref. 18 with revision)

such as alginate or polymers like poly-glycolide-colactide, have also been tested as cell scaffolds. Application of cardiomyocytes derived from embryonic stem (ES) cells has been reported, where improvements in heart remodeling and function were observed after transplantation[13]. However, their use still presents some drawbacks such as the lack of control for a homogenous seeding and distribution of the cells. To solve this problem, new strategies like microtemplating or electrospinning have been incorporated in order to create scaffolds that mimic the natural heart extracellular matrix. A study has reported the creation of a poly(2-hydroxyethyl methacrylate-co-methacrylic acid) hydrogel construct organized as parallel channels that can direct an aligned cardiomyocyte distribution[14].

Cell sheet technology with temperature-responsive culture surface

Another promising approach for fair engraftment and construction of 3D tissue-like structure is the creation of cell sheets or patches without scaffold support. With this approach, inflammatory reactions against the biomaterials constituting the scaffolds would be avoided. Stevens et al. reported a transplantation experiment of scaffold-free and vascularized human cardiac muscle tissue patches including human embryonic stem cell (ESC)-derived cardiomyocytes and endothelial cells which were created by rotating orbital shaker-based cell culture[15].

The generation of cell sheets using two-dimensional cell culture is more promising because of larger scalability and accessibility. This technique has been made possible by using a culture dish covalently grafted with temperature-responsive polymer poly (N-isopropylacrylamide) (PIPAAm) which enables the preparation of cell sheets without enzymatic digestion[16]. The beneficial potential of this technique has been demonstrated by many experiments of stem cell therapy such as the transplantation of a monolayer of adipose tissue-derived MSCs to the infarcted rat heart[17]. Recently, we have reported a transplantation study of a three-

layered cardiac tissue sheet bioengineered with ESC-derived defined cardiac cell populations in the infarcted heart (Fig.1)[18]. In both cases, an increase in tissue neovascularization together with a positive attenuation of heart remodeling responsible for the improvement in cardiac function has been demonstrated. Furthermore, our report showed a cell sheet-based method for prospective elucidation of the cellular mechanisms of cardiac restoration. The combinations of cell types composing the transplanted cell sheets enabled us to elucidate the regenerative function of each cell type (for example, the comparison of cell sheets with or without cardiomyocytes is helpful for the elucidation of the cellular function of cardiomyocytes). This cell-type controlled analysis led us to identify one of the cellular mechanisms of cardiac restoration following cell therapy, namely, that cardiomyocytes are essential for the functional improvement through neovascularization (Fig.2). These results indicate that the tissue-like cell sheet system is useful for the elucidation of cardiac regenerative mechanism as well as for therapeutic purposes. The cell sheet transplantation would be one of the best approaches for cardiac restorative therapy, at least for sub-acute myocardial infarction which might be restored through potent paracrine effects.

Another promising technology for collecting scaffold-free cell sheets is reported using fibrin polymer coated culture dishes. The fabricated cell sheets from neonatal rat cardiomyocytes were transplanted onto the heat-injured rats, and demonstrated successful electrical integration between host heart and cell sheet postoperatively[19]. A novel magnetic force-based cell sheet technology was also developed, and human MSC-derived cell sheet recently showed therapeutic effects for mouse hind limb ischemia[20].

Combination of cell therapy and sustained release of growth factors

The beneficial effects of cell therapy must be further advanced before this therapy attains its full potential. The combination of cell therapy and local protein administration which induces paracrine mechanisms, such as angiogenesis, is one direction for the enhancement of its therapeutic potential. Tabata et al. have developed a sustained release system of angiogenic cytokines, such as basic fibroblast growth factor (bFGF), with biodegradable material, gelatin hydrogel, which enables us to control the release of cytokines during required periods for efficient clinical outcome[21]. The sustained release system of bFGF was applied together with the transplantation of cardiosphere-derived cardiac progenitor cells for porcine MI model with the enhanced functional benefit[22], and with the ongoing clinical trial, ALCADIA[23]. Thus, the drug delivery system using biodegradable biomaterials would be a promising strategy for the advances of cardiac regeneration with cell therapy.

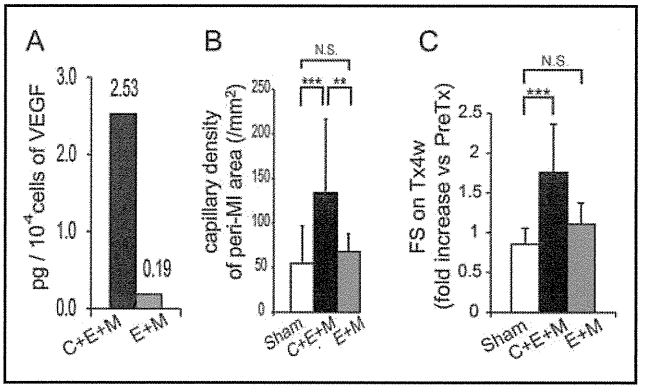

Fig.2 Cell type-controlled sheet analyses
(A): ELISA for VEGF secretion (picogram per10^4 cells) in culture supernatants of C+E+M and E+M sheets. (B,C): Transplantation of sham operation (n=9) versus C+E+M sheets (n=9) versus E+M sheets (n=3) (Tx-d28). (B): Capillary density in peri-MI area (capillary number per square millimeter). (15 views each). (C): Fractional shortening (FS) on echocardiogram (fold increase vs. PreTx). $**p < 0.01$, and $***p < 0.001$ (unpaired t test). C: cardiomyocytes, E: endothelial cells, M: vascular mural cells. N.S., not significant; VEGF, vascular endothelial cell growth factor. (quote from ref. 18 with revision).

Other approaches

It has been recently shown that transplantation of in-vitro created 3D cardiospheres improves engraftment of the cardiac progenitors and the in vivo differentiation towards cardiac and vascular cells[24]. Furthermore, the use of decellularized tissues as scaffold for cell transplantation has also been explored. Different tissues such as the bovine pericardium[25] and omental wrapping[26, 27] have been also used as a support for different cell types like the mesenchymal cells, with the purpose to improve their paracrine effect. Suzuki et al. reported that the concomitant omental wrapping with myocardial cell sheet transplantation for rat myocardial infarction model enhanced the effects of cell transplantation mainly due to promoted neovascularization[28]. However, hurdles still remain for achieving cardiac cell sources with no immunological risk, and for creat-

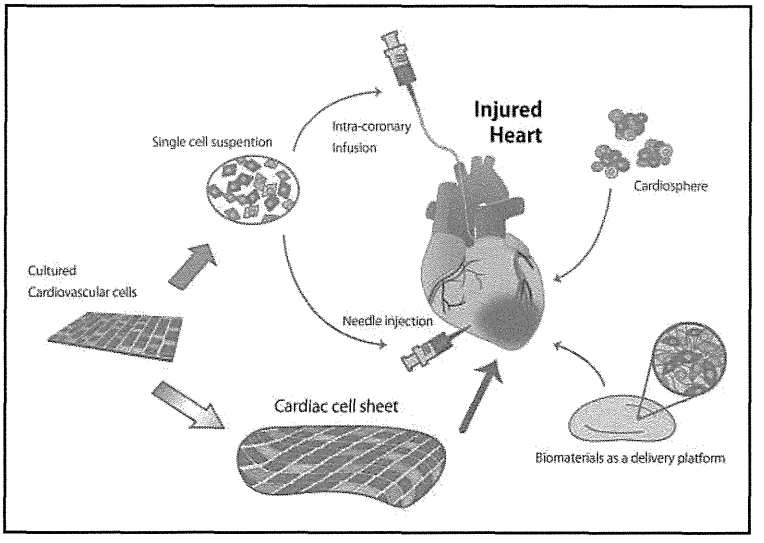

Fig.3 Various methods for cardiac cell transplantation
Efficient cell delivery is essential to maximize the therapeutic potential of cell transplantation.

ing patches/organs that can mimic the structure and function of the heart.

Conclusion

In this review, we have introduced various strategies for fair engraftment of the transplanted cells after cardiac cell therapy to achieve more efficient outcome (Fig.3). We sincerely expect that these advanced modalities with bioengineering technologies would largely enhance the efficacy of cardiac cell therapy and further contribute to cardiac regenerative medicine.

Acknowledgments

We thank our colleagues and laboratory members for their excellent experimental assistance and stimulating discussions. We thank S. Katayama (Kyoto University, Kyoto, Japan) for editing the figures. We thank Dr. M. Takahashi (Kyoto University, Kyoto, Japan) for critical reading of the manuscript.

Source of funding

None

Disclosure of potential conflicts of interest

None

References

1) Sakata R, Fujii Y, Kuwano H: Thoracic and cardiovascular surgery in Japan during 2009: annual report by the Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg. 2011; 59: 636-667.
2) Joggerst SJ, Hatzopoulos AK: Stem cell therapy for cardiac repair: benefits and barriers. Expert Rev Mol Med. 2009; 11: e20.
3) Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P: Bone marrow cells regenerate infarcted myocardium. Nature. 2001; 410: 701-705.
4) Sakakibara Y, Tambara K, Lu F, Nishina T, Sakaguchi G, Nagaya N, Nishimura K, Li RK, Weisel RD, Komeda M: Combined procedure of surgical repair and cell transplantation for left ventricular aneurysm: an experimental study. Circulation. 2002; 106: I193-I197.
5) Chien KR: Regenerative medicine and human models of human disease. Nature. 2008; 453: 302-305.
6) Pelacho B, Mazo M, Gavira JJ, Prósper F: Adult stem cells: from new cell sources to changes in methodology. J Cardiovasc Transl Res. 2011; 4: 154-160.
7) Müller-Ehmsen J, Whittaker P, Kloner RA, Dow JS, Sakoda T, Long TI, Laird PW, Kedes L: Survival and development of neonatal rat cardiomyocytes transplanted into adult myocardium. J Mol Cell Cardiol. 2002; 34: 107-116.
8) Teng CJ, Luo J, Chiu RC, Shum-Tim D: Massive mechanical loss of microspheres with direct intramyocardial injection in the beating heart: implications for cellular cardiomyoplasty. J Thorac Cardiovasc Surg. 2006; 132: 628-632.
9) Cortes-Morichetti M, Frati G, Schussler O, Duong Van Huyen JP, Lauret E, Genovese JA: Association between a cell-seeded collagen matrix and cellular

cardiomyoplasty for myocardial support and regeneration. Tissue Eng. 2007; 13: 2681-2687.
10) Christman KL, Lee RJ: Biomaterials for the treatment of myocardial infarction. J Am Coll Cardiol. 2006; 48: 907-913.
11) Simpson D, Liu H, Fan TH, Nerem R, Dudley SC Jr: A tissue engineering approach to progenitor cell delivery results in significant cell engraftment and improved myocardial remodeling. Stem Cells. 2007; 25: 2350-2357.
12) Zimmermann WH, Melnychenko I, Wasmeier G, Didié M, Naito H, Nixdorff U, Hess A, Budinsky L, Brune K, Michaelis B, Dhein S, Schwoerer A, Ehmke H, Eschenhagen T: Engineered heart tissue grafts improve systolic and diastolic function in infarcted rat hearts. Nat Med. 2006; 12: 452-458.
13) Caspi O, Lesman A, Basevitch Y, Gepstein A, Arbel G, Habib IH, Gepstein L, Levenberg S: Tissue engineering of vascularized cardiac muscle from human embryonic stem cells. Circ Res. 2007; 100: 263-272.
14) Madden LR, Mortisen DJ, Sussman EM, Dupras SK, Fugate JA, Cuy JL, Hauch KD, Laflamme MA, Murry CE, Ratner BD: Proangiogenic scaffolds as functional templates for cardiac tissue engineering. Proc Natl Acad Sci U S A. 2010; 107: 15211-15216.
15) Stevens KR, Kreutziger KL, Dupras SK, Korte FS, Regnier M, Muskheli V, Nourse MB, Bendixen K, Reinecke H, Murry CE: Physiological function and transplantation of scaffold-free and vascularized human cardiac muscle tissue. Proc Natl Acad Sci U S A. 2009; 106: 16568-16573.
16) Okano T, Yamada N, Sakai H, Sakurai Y: A novel recovery system for cultured cells using plasma-treated polystyrene dishes grafted with poly (N-isopropylacrylamide). J Biomed Mater Res. 1993; 27: 1243-1251.
17) Miyahara Y, Nagaya N, Kataoka M, Yanagawa B, Tanaka K, Hao H, Ishino K, Ishida H, Shimizu T, Kangawa K, Sano S, Okano T, Kitamura S, Mori H: Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. Nat Med. 2006; 12: 459-465.
18) Masumoto H, Matsuo T, Yamamizu K, Uosaki H, Narazaki G, Katayama S, Marui A, Shimizu T, Ikeda T, Okano T, Sakata R, Yamashita JK: Pluripotent stem cell-engineered cell sheets re-assembled with defined cardiovascular populations ameliorate reduction in infarct heart function through cardiomyocyte-mediated neovascularization. Stem Cells. 2012; 30: 1196-1205.
19) Furuta A, Miyoshi S, Itabashi Y, Shimizu T, Kira S, Hayakawa K, Nishiyama N, Tanimoto K, Hagiwara Y, Satoh T, Fukuda K, Okano T, Ogawa S: Pulsatile cardiac tissue grafts using a novel three-dimensional cell sheet manipulation technique functionally integrates with the host heart, in vivo. Circ Res. 2006; 98: 705-712.
20) Ishii M, Shibata R, Numaguchi Y, Kito T, Suzuki H, Shimizu K, Ito A, Honda H, Murohara T: Enhanced angiogenesis by transplantation of mesenchymal stem cell sheet created by a novel magnetic tissue engineering method. Arterioscler Thromb Vasc Biol. 2011; 31: 2210-2215.
21) Tabata Y: Tissue regeneration based on growth factor release. Tissue Eng 2003; 9: S5-S15.
22) Takehara N, Tsutsumi Y, Tateishi K, Ogata T, Tanaka H, Ueyama T, Takahashi T, Takamatsu T, Fukushima M, Komeda M, Yamagishi M, Yaku H, Tabata Y, Matsubara H, Oh H: Controlled delivery of basic fibroblast growth factor promotes human cardiosphere-derived cell engraftment to enhance cardiac repair for chronic myocardial infarction. J Am Coll Cardiol. 2008; 52: 1858-1865.
23) AutoLogous human CArdiac-Derived stem cell to treat Ischemic cArdiomyopathy (ALCADIA) trial. http://clinicaltrials.gov/ct2/show/ NCT00981006 (accessed Jul 12, 2012).
24) Bartosh TJ, Wang Z, Rosales AA, Dimitrijevich SD, Roque RS: 3D-model of adult cardiac stem cells promotes cardiac differentiation and resistance to oxidative stress. J Cell Biochem. 2008; 105: 612-623.
25) Wei HJ, Chen CH, Lee WY, Chiu I, Hwang SM, Lin WW, Huang CC, Yeh YC, Chang Y, Sung HW: Bioengineered cardiac patch constructed from multilayered mesenchymal stem cells for myocardial repair. Biomaterials. 2008; 29: 3547-3556.
26) Ueyama K, Bing G, Tabata Y, Ozeki M, Doi K, Nishimura K, Suma H, Komeda M: Development of biologic coronary artery bypass grafting in a rabbit model: revival of a classic concept with modern biotechnology. J Thorac Cardiovasc Surg. 2004; 127: 1608-1615.
27) Shudo Y, Miyagawa S, Fukushima S, Saito A, Shimizu T, Okano T, Sawa Y: Novel regenerative therapy us-

ing cell-sheet covered with omentum flap delivers a huge number of cells in a porcine myocardial infarction model. J Thorac Cardiovasc Surg. 2011; 142: 1188-1196.

28) Suzuki R, Hattori F, Itabashi Y, Yoshioka M, Yuasa S, Manabe-Kawaguchi H, Murata M, Makino S, Kokaji K, Yozu R, Fukuda K: Omentopexy enhances graft function in myocardial cell sheet transplantation. Biochem Biophys Res Commun. 2009; 387: 353-359.

Gen Thorac Cardiovasc Surg (2013) 61:61–66
DOI 10.1007/s11748-012-0198-9

CURRENT TOPICS REVIEW ARTICLE

Perioperative control of blood glucose level in cardiac surgery

Kenji Minakata · Ryuzo Sakata

Received: 9 August 2012 / Published online: 5 January 2013

Abstract It is well recognized that poor perioperative blood glucose (BG) control can increase the risk of infection, cardiovascular accidents, and even death in patients undergoing cardiac surgery. Since it has been reported that tight BG control (80–110 mg/dL) yields better outcomes in critically ill patients, it became a standard of care to control BG using intravenous insulin infusion in ICU. However, it has been debated in terms of the optimal target range whether a strict control with intensive insulin therapy is better than liberal control. Because strict BG control can often cause hypoglycemia, which in turn increases the hospital mortality. In fact, a meta-analysis of randomized clinical trials concluded that tight BG control was not associated with significantly reduced hospital mortality but was associated with an increased risk of hypoglycemia. According to the current published guidelines, it seems to be optimal to control BG level of 140–180 mg/dL in ICU. In terms of more strict BG control (110–140 mg/dL), it may be appropriate in selected patients as long as this can be achieved without significant hypoglycemia.

Keywords Blood glucose level · Cardiac surgery · Diabetes mellitus · Infection · Mortality

The review was submitted at the invitation of the editorial committee.

K. Minakata (✉) · R. Sakata
Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: minakata@kuhp.kyoto-u.ac.jp

Introduction

Physical stress induces a number of neuro-hormonal responses to maintain or increase blood glucose (BG) level (part of the "fight or flight" response). This is especially true in cardiac surgery, which often involves one of the most invasive and stressful procedures in modern medicine: cardiopulmonary bypass. However, in diabetic patients or others with glucose intolerance, the BG level may increase beyond the optimal range, causing hyperglycemia. During or immediately after surgery, hyperglycemia can cause numerous complications: abnormal immune response, vascular malfunction, metabolic acidosis and even coma. Perhaps one of the most noteworthy complications is the increased rate of infection, including deep sternal wound infection (DSWI). It is well known that poor BG control perioperatively can increase the incidence of DSWI, which can easily lead to sepsis, multi-organ failure and even death. In this review, the dangers of perioperative hyperglycemia are discussed, and the most recent strategies for perioperative BG control are summarized based on the findings of large clinical trials.

The diabetic disadvantage

The prevalence of diabetes mellitus (DM) has increased dramatically in Western countries over the last several decades, leading in turn to increased mortality due to cardiovascular events [1]. This trend is also apparent in Asian countries, especially in Japan, where the number of DM patients has increased from 6.9 to 8.9 million (approximately 7 % of the general population) in the last decade (a 29 % increase) [2]. The most important life-threatening complication in DM patients is obviously coronary artery disease [3]. There has been debate regarding the optimal

treatment for DM patients with coronary artery disease. Some favor percutaneous catheter intervention (PCI), while others favor coronary artery bypass grafting (CABG). Some studies have shown that CABG yields better long-term outcomes in DM patients with multivessel disease [4, 5]. Despite the recent technological advances in PCI, such as drug-eluting stents, CABG remains the treatment of choice in many DM patients.

We recently conducted a large multi-institutional clinical study in Japanese patients undergoing isolated CABG, and reported that DM was associated with higher incidence of infection and higher mortality [6]. The overall infection rate was 9.2 % in DM patients versus 6.1 % in non-DM patients ($p = 0.036$). In addition, the hospital mortality rate was 2.1 % in DM patients versus 1.1 % in non-DM patients ($p = 0.124$). These results were consistent with the others based on the STS database analyses. In fact, it has been reported that DM in patients undergoing open heart surgery poses a significant risk for hospital mortality and morbidity, including stroke, DSWI and increased length of hospital stay [7]. This report found that DM patients were significantly more likely to die within 30 days following any of the cardiac procedures included in the study. In fact, the 30-day mortality in DM patients versus non-DM patients were as follows: 3.96 versus 2.82 % for isolated CABG; 6.63 versus 3.57 % for AVR; and 11.07 versus 5.52 % for MVR, respectively (all differences significant with p values <0.001). Likewise, the stroke rates for DM patients versus non-DM patients were as follows: 2.22 versus 1.40 % for isolated CABG; 2.74 versus 1.44 % for AVR; 3.64 versus 1.94 % for MVR (all differences significant with p <0.001) [7]. In addition, DM patients have worse long-term survival than non-DM patients after surgery [8]. The survival rate of DM patients after CABG and/or valve replacement was twice as poor as that of non-DM patients [7]. There is no doubt that DM patients have unfavorable baseline characteristics such as diffuse coronary artery disease, peripheral artery disease, high body mass index, and worse preoperative renal function, all of which could contribute to worse short- and long-term outcomes as compared to non-DM patients.

Deep sternal wound infection (anterior mediastinitis)

Although surgical site infection is one of the most common postoperative complications, especially in DM patients, DSWI (anterior mediastinitis) has a profound impact on early and late morbidity and mortality. Our previous study showed that the incidence of DSWI was 2.0 % in DM patients versus 1.1 % in non-DM patients, which was highly likely related with increased hospital mortality [6]. Likewise, according to the STS database analyses, DM patients had nearly twice the incidence of DSWI compared to non-DM patients. Figures for specific procedures were as follows: 1.02 versus 0.45 % for isolated CABG; 0.78 versus 0.41 % for AVR; and 0.72 versus 0.35 % for MVR (all differences significant with p values <0.001) [7]. DSWI definitely increases the mortality rate, as well as increasing the length of hospital stay and associated costs. In 1997, Zerr et al. [9] reported that hyperglycemia in the first 2 postoperative days in DM patients undergoing cardiac surgery is a significant independent predictor of DSWI.

Metabolic consequences of hyperglycemia in DM patients

Free fatty acids are the primary energy substrate in the non-ischemic myocardium [10]. In fact, long-chain fatty acids provide more than six times as much energy as the oxidation of an equal amount of glucose. Under ischemic conditions, glucose becomes the primary energy source in the myocardium so that the ischemic myocardium can more effectively utilize the limited supply of oxygen to preserve cellular integrity and contractile function. This metabolic shift prevents the increase of toxic products of fatty acids such as oxygen free radicals and it plays an important role in myocardial and vascular preservation. In DM patients, however, glucose uptake and/or transport function is impaired, which forces the myocardium to rely heavily on free fatty acid metabolism as its primary energy source. As a result, the level of free fatty acids and their metabolism is increased, contributing to an increased level of toxic substrates leading to myocardial and vascular dysfunction. These detrimental effects are accelerated during the period of myocardial ischemia that occurs under aortic cross-clamping during cardiac surgery in DM patients.

Effects of intravenous insulin infusion in cardiac surgery

Several animal and human studies have reported that intravenous insulin reverses the metabolic dysfunctions associated with DM via several mechanisms, such as stimulation of myocardial glucose utilization, and anti-inflammatory/antioxidant effects on a cellular and molecular level [10]. This may be the reason why continuous insulin infusion, in addition to normoglycemia, improves clinical outcomes in patients with acute coronary syndrome and CABG. Lazar et al. [10] demonstrated that BG control (serum glucose: 125–200 mg/dL) with glucose-insulin-potassium solution in patients with DM undergoing CABG improved perioperative outcomes, enhanced survival, and decreased the incidence of ischemic events and wound complications. They suggested that the presence of insulin itself is important to improve the metabolism in DM patients, in addition to maintaining normal glucose levels [11].

Impact of perioperative BG control in cardiac surgery

Based on a large prospective observational study, Furnary et al. [12] reported that there was a highly significant relationship between mortality and postoperative BG levels rising above 175 mg/dL. Dr. Furnary is in charge of the Portland Diabetic Project, which is an ongoing prospective study of over 5,000 DM patients, which aims to show that tight glucose control from the end of surgery until the 2nd postoperative day with continuous insulin infusion may eliminate the diabetic disadvantage [13]. His group found that tight glucose control with a full 3 days of continuous insulin infusion (which they termed "the Portland Protocol") significantly reduced mortality (by 65 %), DSWI (by 63 %), and length of hospital stay (average 2-day reduction). They concluded that DM is not a true risk factor for the diabetic disadvantage in terms of increased mortality and morbidity when the perioperative BG level is well controlled within a certain range according to their protocol. The usefulness of perioperative BG control with intravenous insulin was also shown in patients undergoing off-pump CABG [14].

How to control the BG level in a timely and effective manner with insulin: intermitted subcutaneous injection or continuous intravenous infusion?

There is no doubt that insulin therapy has been the standard treatment for controlling BG in the acute clinical setting. Traditionally, regular insulin was given subcutaneously every 4–6 h according to a certain sliding scale to control BG in the ICU or ward. In the late 1990 s, however, Furnary et al. [15] reported that continuous intravenous insulin infusion yielded better BG control than intermittent subcutaneous injection and led to a significant reduction in DSWI in patients undergoing cardiac surgery. Since that time, a number of continuous insulin infusion protocols have been proposed with different target ranges in different clinical settings [16].

Preoperative BG control

DM patients undergoing cardiac surgery may have different levels of diabetic control preoperatively. As a marker of the level of BG control, hemoglobin A1c is very useful because it indicates the level of BG for the previous 4–12 weeks. In patients, where their level of hemoglobin A1c indicates poor levels of BG control, the physician is faced with a dilemma: should he or she wait until the hemoglobin A1c level improves before attempting surgery? Halkos et al. [17] reported that an elevated hemoglobin A1c level (≥7.0 %) was strongly associated with adverse postoperative events such as myocardial infarction, DSWI, renal failure and cerebrovascular incidents after CABG. These adverse events are likely due to the higher associated comorbidities, such as systemic hypertension, advanced chronic kidney disease and/or peripheral artery disease in patients with high hemoglobin A1c. They recommended that in patients with hemoglobin A1c greater than 8.7 % and not requiring urgent or emergency CABG, consideration should be given to achieving good BG control before surgery to minimize morbidity and mortality. On the other hand, Furnary et al. did not identify the level of preoperative hemoglobin A1c as an independent significant predictor of mortality, DSWI or length of hospital stay. They only found that preoperative BG level is a risk factor for DSWI and increased length of hospital stay. Therefore, they recommended controlling the preoperative BG level, not the level of hemoglobin A1c. In other words, they did not recommend waiting until the hemoglobin A1c is improved before surgery as long as BG is strictly controlled from the day of surgery to the 2nd postoperative day (three full days) with continuous intravenous insulin infusion [13]. In general, it should be carefully screened if there are any significant indicators of poor preoperative BG control, such as highly elevated HbA1c, elevated amount of urine glucose (10 g/day), and presence of ketone bodies in urine in elective operations.

Intraoperative BG control: is it necessary?

There have been a few studies on BG control during cardiac surgery. Doenst et al. [18] reported that a high glucose level during cardiopulmonary bypass was an independent predictor of mortality in both DM and non-DM patients. They also found that a high glucose level during cardiopulmonary bypass was also an independent predictor of all major adverse events in both patient groups. In addition, Ghandi et al. [19] reported, in a retrospective observational study on 409 cardiac surgical patients, that intraoperative hyperglycemia was an independent risk factor for perioperative complications, including mortality, after adjustment for postoperative glucose concentrations. Each 20 mg/dL increase in glucose concentration greater than 100 mg/dL during surgery was associated with a 34 % increase in the likelihood of postoperative complications. However, they subsequently conducted the first prospective randomized study on 400 DM and non-DM patients undergoing on-pump CABG and showed that intraoperative intensive insulin therapy with a target range of 80–100 mg/dL did not reduce perioperative mortality and morbidity, but rather increased stroke rate and mortality [20]. As long as the BG level is in the liberal range (≤200 mg/dL) during cardiac surgery, it may not be beneficial to attempt strict BG control. Also, caution needs to be taken to prevent profound hypoglycemia when insulin is given intravenously during

anesthesia. It has been shown that attempting to maintain normoglycemia in the setting of insulin infusion may initiate postoperative hypoglycemia, potentially causing adverse events [21].

The optimal target range of the BG level in the ICU: is strict control better than liberal control?

The definitions of "tight," "strict" and "intensive" BG control tend to differ in each report, and it has been debated what target range is optimal. In addition, it should be noted with caution that the target does not always reflect the actual level achieved. In a landmark paper, Van den Berghe et al. [22] conducted the first prospective randomized trial comparing tight BG control (target 80–110 mg/dL) with intensive insulin therapy to conventional BG control (180–200 mg/dL) in critically ill surgical patients. This study included over 1,500 patients, 63 % of whom had undergone cardiac surgery before ICU admission. They found that tight BG control resulted in a significant reduction in mortality (10.6 % with intensive treatment vs. 20.2 % with conventional treatment, $p = 0.005$) in patients who required ≥5 days of ICU care with multiorgan failure and sepsis. In addition, cardiac surgical mortality was reduced in those patients requiring ≥5 days of ICU care with other conditions. D'Alessandro et al. [23] published a propensity analysis that showed that strict BG control significantly reduced the EuroSCORE expected mortality in DM patients undergoing CABG, especially in moderate to high-risk patients. Their BG target in the ICU was ≤140 mg/dL. In terms of long-term outcomes, Lazar et al. [11] showed that tight perioperative glucose control (125–200 mg/dL) with glucose-insulin-potassium solution improved not only perioperative outcomes, but also long-term survival and freedom from recurrent angina comparing to the standard therapy (<250 mg/dL). Based on these studies, it is logical to conclude that it is beneficial to maintain BG at less than 180–200 mg/dL to decrease postoperative morbidity and mortality.

Of course, this begs the question: Exactly how low should the target be? Since the aforementioned landmark paper by Van den Berghe et al., it has been widely accepted that tight BG control with intensive insulin therapy (80–110 mg/dL) is better than conventional control in surgery or in the ICU. However, following this report, several randomized trials failed to show the benefit of tight BG control with intensive insulin therapy. In addition, a meta-analysis of 29 randomized studies focusing on the benefits and risks of tight glucose control (very tight: ≤110 mg/dL or moderately tight: <150 mg/dL) in critically ill adult patients concluded that tight glucose control was not associated with significantly reduced hospital mortality, but was associated with an increased risk of hypoglycemia [24]. To support these results, a recent large prospective randomized multicenter trial (the NICE-SUGAR study) demonstrated that intensive BG control with a target of 81–108 mg/dL increased mortality among adults in the ICU compared with conventional BG control with a target of 180 mg/dL or less [25]. This study involved over 6,000 patients, however, the mortalities in the intensive control group and conventional control group were 27.5 and 24.9 % at 90 days after randomization, respectively. In both groups, potentially life-sustaining treatments were withheld or withdrawn in more than 90 % of the patients who died. In addition, it seems that severe hypoglycemia commonly occurred in the intensive BG control group of the study (6.8 %), which raises the question of the safety and feasibility of the tight glucose control protocol itself. It has clearly been shown that hypoglycemia is associated with mortality in the ICU setting [26]. Because the patients in the study were so sick at the time of enrollment, it is difficult to compare the results of this study with studies on regular cardiac surgery patients, given the current acceptable mortality after CABG of around 1–2 %. Based on a large CABG cohort, Bhamidipati et al. reported that moderate glycemic control (127–179 mg/dL) was superior to tight (≤126 mg/dL) or liberal (≥180 mg/dL) glycemic control, with decreased mortality and fewer major complications [27]. They concluded that moderate control is ideal for the DM patients undergoing CABG. It may be necessary to conduct a prospective randomized study to compare tight glucose control and conventional glucose control using more sophisticated protocols with a minimum risk of hypoglycemia in exclusively cardiac surgery patients to reach a definitive conclusion.

Is BG variability more important than BG level?

Some studies have shown that variability (wide vacillation) in BG levels is more important than the achieved BG level in terms of outcomes. Egi et al. [28] using a large multicenter cohort of patients and set of glucose measurements, found that the variability of BG was an independent predictor of ICU and hospital mortality, and that its predictive ability was greater than that of the mean BG level. In addition, Hermanides et al. [29] reported that high BG variability was closely associated with ICU and in-hospital death, and also that high BG variability combined with high mean BG values was associated with highest ICU mortality. They concluded that in patients who underwent strict glycemic control, low BG variability seemed protective, even when mean BG levels remained elevated.

Current published recommendations for perioperative control of BG levels

The American Diabetes Association published guideline for the medical care of diabetes patients in 2012 [30]. According to these guidelines, in critically ill patients in

the hospital, insulin therapy should be initiated for the treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL. Also, once insulin therapy is started, a glucose range of 140–180 mg/dL is recommended for the majority of these patients. With regard to more strict control (110–140 mg/dL), it may be appropriate in selected patients as long as this can be achieved without significant hypoglycemia.

The STS guidelines recommend that patients with and without diabetes with persistently elevated serum glucose ($\geq$180 mg/dL) should receive IV insulin infusions to maintain serum glucose $\leq$180 mg/dL for the duration of their ICU care. All patients who require three or more days in the ICU because of ventilator dependency, the need for inotropes, intra-aortic balloon pumps, left ventricular assist device support, antiarrhythmics, dialysis, or continuous veno-venous hemofiltration, should receive a continuous insulin infusion to keep BG at $\leq$150 mg/dL, regardless of their diabetic status. Also, before intravenous insulin infusion is discontinued, patients should be transitioned to a subcutaneous insulin schedule using institutional protocols [31]. The American College of Physicians Guidelines also recommends a target BG level of 140–200 mg/dL in medical/surgical ICU patients with hyperglycemia [32]. It does not recommend intensive insulin therapy because of the high likely hood of hypoglycemia.

Conclusions

In conclusion, hyperglycemia during and/or after cardiac surgery entails several risks, such as an increased risk of infection, stroke, and myocardial or vascular dysfunction. Therefore, BG levels should be maintained at 140–180 mg/dL with continuous insulin infusion.

References

1. Bonow RO, Gheorghiade M. The diabetes epidemic: a national and global crisis. Am J Med. 2004;116 Suppl 5A:2S–10S.
2. Annual report from the national survey of life and nutrition 2007, the Ministry of Health, Labour and Welfare of Japan (Japanese). http://www.mhlw.go.jp/houdou/2008/12/h1225-5.html.
3. Flaherty JD, Davidson CJ. Diabetes and coronary revascularization. JAMA. 2005;293:1501–8.
4. Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. Circulation. 2004;109:2290–5.
5. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet. 2009;373:1190–7.
6. Minakata K, Bando K, Takanashi S, Konishi H, Miyamoto Y, Ueshima K, et al. Impact of diabetes mellitus on outcomes in Japanese patients undergoing coronary artery bypass grafting. J Cardiol. 2012;59:275–84.
7. Brown JR, Edwards FH, O'Connor GT, Ross CS, Furnary AP. The diabetic disadvantage: historical outcomes measures in diabetic patients undergoing cardiac surgery—the pre-intravenous insulin era. Smin Thorac Cardiovasc Surg. 2006;18:281–8.
8. Szabó Z, Håkanson E, Svedjeholm R. Early postoperative outcome and medium-term survival in 540 diabetic and 2239 nondiabetic patients undergoing coronary artery bypass grafting. Ann Thorac Surg. 2002;74:712–9.
9. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann Thorac Surg. 1997;63:356–61.
10. Lazar HL. Alterations in myocardial metabolism in the diabetic myocardium. Sem Thorac Cardiovasc Surg. 2006;18:289–92.
11. Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation. 2004;109:1497–502.
12. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2003;125:1007–21.
13. Furnary AP, Wu Y. Eliminating the diabetic disadvantage: the Portland Diabetic Project. Semin Thorac Cardiovasc Surg. 2006;18:302–8.
14. Fujii T, Watanabe Y, Shiono N, Kawasaki M, Yokomuro H, Ozawa T, et al. Usefulness of perioperative blood glucose control in patients undergoing off-pump coronary artery bypass grafting. Gen Thorac Cardiovasc Surg. 2007;55:409–15.
15. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg. 1999;67:352–60.
16. Kelly JL, Hirsch IB, Furnary AP. Implementing an intravenous insulin protocol in your practice: practical advice to overcome clinical, administrative, and financial barriers. Semin Thorac Cardiovasc Surg. 2006;18:346–58.
17. Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Kerendi F, Song HK, et al. Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2008;136:631–40.
18. Doenst T, Wijeysundera D, Karkouti K, Zechner C, Maganti M, Rao V, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2005;130:1144.
19. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, Williams BA, et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clin Proc. 2005;80:862–6.
20. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med. 2007;146:233–43.
21. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Attempting to maintain normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative hypoglycemia. Anesth Analg. 1999;89:1091–5.
22. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359–67.
23. D'Alessandro C, Leprince P, Golmard JL, Ouattara A, Aubert S, Pavie A, et al. Strict glycemic control reduces EuroSCORE

expected mortality in diabetic patients undergoing myocardial revascularization. J Thorac Cardiovasc Surg. 2007;134:29–37.
24. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008;300:933–44.
25. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
26. Hermanides J, Bosman RJ, Vriesendorp TM, Dotsch R, Rosendaal FR, Zandstra DF, et al. Hypoglycemia is associated with intensive care unit mortality. Crit Care Med. 2010;38:1430–4.
27. Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL, et al. Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2011;141:543–51.
28. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006;105:244–52.
29. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. Crit Care Med. 2010;38:838–42.
30. American Diabetes Association. Executive summary: standards of medical care in diabetes—2012. Diabetes Care. 2012;35(Suppl 1):S4–10.
31. Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR, et al. The Society of Thoracic Surgeons Practice Guideline Series: blood glucose management during adult cardiac surgery. Ann Thorac Surg. 2009;87:663–9.
32. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P, The clinical Guidelines Committee of the American College of Physicians. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2011;154:260–7.

World Journal of Cardiovascular Surgery, 2013, 3, 8-14
doi:10.4236/wjcs.2013.31002 Published Online March 2013 (http://www.scirp.org/journal/wjcs)

Scientific Research

Ventricular Approach for Functional Mitral Regurgitation in Cardiomyopathy

Kenji Minakata*, Kazuhiro Yamazaki, Senri Miwa, Masaki Funamoto, Motoyuki Kumagai, Akira Marui, Ryuzo Sakata

Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan
Email: *minakata@kuhp.kyoto-u.ac.jp

Received December 19, 2012; revised January 24, 2013; accepted February 5, 2013

ABSTRACT

Background: The key mechanism of functional mitral regurgitation (FMR) in cardiomyopathy is leaflet tethering caused by displacement of the papillary muscles (PM) due to left ventricular dilatation. The attendant remodeling process is characterized by intraventricular widening between both PM. Recently, surgical ventricular restoration (SVR) has been proposed as a technique to reduce leaflet tethering by improving ventricular geometry. However, it is unknown how SVR improve FMR. **Methods and Results:** From 2003 to 2010, we surgically treated FMR in 100 patients with idiopathic dilated cardiomyopahy (DCM) or ischemic cardiomyopathy (ICM). Of those, we performed posterior wall exclusion procedures by either resection (the Batista procedure, n = 13) or plication (n = 19) to approximate papillary muscle distance in a total of 32 patients (DCM in 17, ICM in 15), and these patients formed the cohort of this study. There were two 30-day mortalities (6.3%). There was no significant change in left ventricular ejection fraction, however, the size of the left ventricle, degree of MR, tethering height and distance of PM significantly decreased after operation and well maintained at the mean follow up of 3.3 ± 2.1 years. **Conclusions:** Posterior wall resection or plication with PM approximation provides excellent reduction of leaflet tethering and MR. Thus, reduction of PM distance may be helpful to treat FMR due to leaflet tethering.

Keywords: Cardiomyopathy; Heart Failure Operations; Mitral Regurgitation; Myocardial Remodeling

1. Introduction

It is increasingly evident that functional mitral regurgitation (FMR) is more likely to recur or persist after mitral annuloplasty if there is severe mitral leaflet tethering in patients with idiopathic dilated cardiomyopathy (DCM) or ischemic dilated cardiomyopathy (ICM) [1]. Several techniques have been proposed to treat FMR, in addition to the common technique of mitral annuloplasty (MAP) using downsized annuloplasty rings. Most of these techniques aim to reduce leaflet tethering, and are thus referred to as "subvalvular procedures." To date, proposed subvalvular techniques used to treat leaflet tethering include: 1) papillary muscle relocation or approximation [2,3]; 2) chordal cutting [4]; and 3) surgical ventricular restoration (SVR) [5]. Each of these techniques can play an important role in reducing leaflet tethering via different mechanisms. As such, it seems practical to use a combination of these techniques [6,7]. We have aggressively treated patients with FMR using different techniques at our institutions [8,9], and herein we report on the early and mid-term outcomes of our series of patients, focusing mainly on posterior wall exclusion procedures.

*Corresponding author.

2. Materials and Methods

2.1. Patient Selection

From June 2003 to May 2010, a total of 100 patients who had FMR associated with either ICM (n = 78) or DCM (n = 22) underwent MAP with various types of SVR procedures at our institutions. The indications for SVR procedures included dilated left ventricle (left ventricular end-diastolic dimension ≥65 mm by echocardiography), presence of MR greater than moderate, and presence of congestive heart failure. According to the size and shape of the left ventricle and its myocardial condition, we performed SVR such as overlapping left ventriculoplasty [6] or septal-anterior wall ventricular exclusion (SAVE) with endocardial patch reconstruction [10] not only for patients with ICM due to a previous antero-septal infarction, but also for those with DCM. The main purpose of these techniques was to reduce the size and to restore the left ventricle to a more ellipsoidal shape. However, we realized that dilatation of the postero-lateral wall accompanied by an increased distance between both papillary

muscles may be a more important cause of mitral leaflet tethering. Thus, we started to use a procedure to reduce inter-papillary muscle distance by excluding the posterior wall. During the study period, a total of 32 patients underwent posterior wall exclusion procedures with either resection (the Batista procedure) or plication accompanied with papillary muscle approximation (PMA). These patients formed the cohort of this study. The mean age was 61.7 ± 12.3 years (50% of patients were at the age ≥65), and male gender was predominant (75%). Preoperatively, all patients underwent coronary angiography, right-side heart catheterization, and myocardial nuclear study whenever feasible. Also, cardiac magnetic resonance study with or without gadolinium enhancement was performed if patients had no permanent pacemakers/defibrillators.

2.2. Echocardiographic Study

All patients underwent transthoracic echocardiography before and after operation. Standard two-dimensional and Doppler examination was performed. In addition to the baseline measurements of left ventricular end-diastole dimension (LVEDD) and end-systolic dimension (LVESD), left ventricular volumes (end-diastolic: LVEDV; end-systolic: LVESV) and ejection fraction (EF) were determined by the modified biplane Simpson's method. Degree of mitral regurgitation was assessed quantitatively using proximal isovelocity surface area and vena contracta method [11]. The effective regurgitant orifice (ERO) and regurgitant volume (RV) were calculated by the formula. Then, severity of MR was defined according to the current guideline as none (Grade 0), mild (Grade 1), moderate (Grade 2), moderately severe (Grade 3) and severe (Grade 4). The surgical indication of mitral valve procedures was a presence of MR greater than moderate (ERO ≥ 20 mm^2 and/or RV ≥ 30 ml). Tethering height was defined as the distance between the plane of the mitral annulus and the coaptation point. This was measured in the mid-systolic parasternal long axis view. The distance between the anterior and posterior papillary muscles was measured with the short-axis view at the level of the papillary muscle insertion to the endocardial surface in end-diastole. Intraoperative transesophageal echocardiography was performed in all the patients to evaluate anatomy, valvular competence and cardiac functions throughout the operation.

2.3. Operative Technique

All procedures were conducted on hearts arrested by antegrade tapid crystalloid cardioplegia, followed by tapid blood cardioplegia every 20-30 minutes. In addition, retrograde blood cardioplegia may be given in patients with severe coronary artery disease. We do not use terminal hot shot. First, complete coronary revascularization was performed when indicated, and additional antegradecardioplegia was given through saphenous vein grafts which are anastomosed to target coronary arteries in those patients. Then, the first incision was made in the anterior myocardial wall close to the apex parallel to the left anterior descending artery. This incision was extended distally beyond the apex and proximally as needed. The anterior and posterior papillary muscles were carefully identified and mitral leaflets were examined. Usually, the distal incision was further extended towards the posterior wall along to the midline of the anterior and posterior papillary muscles (**Figure 1(a)**).

As shown in **Figure 1(b)**, our PMA technique was as follows: two or three pledgeted 3-0 braided polyester sutures were passed through the body and base of the anterior and posterior papillary muscles, and then these sutures were tied so that both papillary muscles sat side by side. These sutures were usually passed through posterior wall of the left ventricle in between both papillary muscles to plicate the posterior wall as well. When the posterior wall was thin and severely dilated, the incision was extended towards the base of the left ventricle about 2cm distal to the coronary sinus, then a small section of the posterior wall was excised as needed (**Figure 1(c)**). Several deep and wide mattress sutures using 4-0 polypropylene sutures supported by felt strips were used to approximate the posterior wall to decrease the inter-papillary muscle distance (the Batista procedure; **Figure 1(d)**). PMA was occasionally performed to secure the alignment of both papillary muscles. The left ventriculotomy was then closed with two layers of sutures.

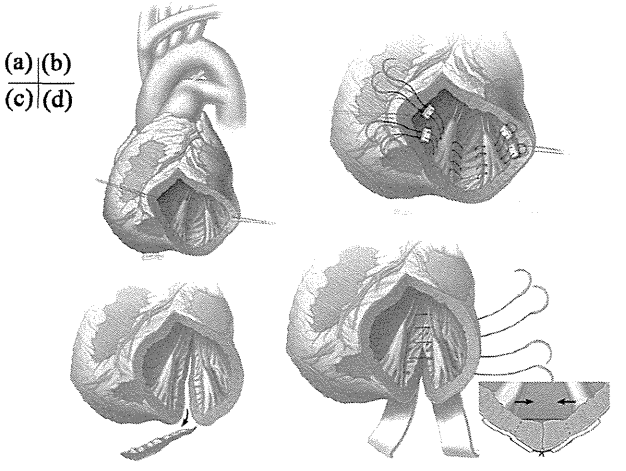

Figure 1. (a) Initial incision of the left ventriculotomy; (b) Papillary muscle approximation with posterior wall plication; (c) The incision is extended posteriorly towards the base of left ventricle; (d) Several deep and wide mattress sutures supported by felt strips are used to approximate the posterior wall to decrease the inter-papillary muscle distance (the Batista procedure).

