

## Review Article

# Application of animal and human PET in cardiac research

Quan Wang<sup>1\*</sup>, Zhi-Gang He<sup>2\*</sup>, Shun-Yuan Li<sup>3</sup>, Mao-Hui Feng<sup>4</sup>, Hong-Bing Xiang<sup>1</sup>

Departments of <sup>1</sup>Anesthesiology and Pain Medicine, <sup>2</sup>Emergency Medicine, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, PR China; <sup>3</sup>Department of Anesthesiology, The First Affiliated Quanzhou Hospital of Fujian Medical University, Quanzhou 362000, PR China; <sup>4</sup>Department of Gastrointestinal Surgery, Zhongnan Hospital, Wuhan University, No. 169 Donghu Road, Wuhan 430071, PR China. \*Equal contributors.

Received February 25, 2018; Accepted April 19, 2018; Epub June 15, 2018; Published June 25, 2018

**Abstract:** Purpose of Review: After a warm-up period of imaging research, several modalities of positron emission tomography (PET) are under development for evaluating ischemic heart disease. Recent Findings: Several types of well-documented stem/progenitor PET imaging have been utilized for changes in myocardial blood flow and carbohydrate metabolism. Some recent experimental and human studies reported that these data may have beneficial effects on cardiac research. Summary: Although the role of PET in the pathology of ischemic heart disease has not been sufficiently elucidated, many studies attempting imaging research of myocardial metabolism and neural regulation have been reported. Further studies are needed to better evaluate the potential of PET in evaluating ischemic heart disease.

**Keywords:** Positron emission tomography, cardiac research, ischemic heart disease

### Introduction

Cardiac ischemia is the serious event in heart surgery. A great need exists for improved formulations and mechanisms to prevent and protect the myocardial tissues from reperfusion damage caused by myocardial ischemia. Current efforts to prevent reperfusion damage to the myocardial tissues, which in many cases leads to myocardial infarction and circulatory arrest [1-3]. The neural regulation is involved in an imbalance in metabolic supply and demand within the ischemic myocardial tissues [4-8], which is a natural prevention from ischemia and reperfusion-associated tissue inflammation and organ dysfunction. Modern imaging, such as positron emission tomography (PET), has revolutionized our view of ischemic heart disease [9-13], allowing the opportunity to investigate the metabolic regulation mechanisms of heart by measuring the changes in myocardial blood flow or carbohydrate metabolism, and to offer potential information to further improve prognostic outcome of ischemic heart disease [14-17].

### Positron-emitting tracers

Today, the field of PET medicine is undergoing great development [18]. Traditionally, there have been several options for positron-emitting tracers, i.e., <sup>15</sup>O-water, <sup>13</sup>N-ammonia and <sup>82</sup>Rubidium. However, some new sources of positron-emitting tracers were successively accumulated, such as <sup>18</sup>F-labeled myocardial flow radiotracer flurpiridaz [14], and the potential for PET in conjunction with several radiotracers seems to be expanding very rapidly. Rapid development of labeling biologic chemistry gives great potential for the development of new PET tracer candidates [15]. It is known that nanoparticle imaging rely on MRI detection of the iron oxide cores [19, 20], and a study of Ueno [21] showed that dextran nanoparticles the PET isotope copper-64 detected heart transplant rejection and predicted organ survival by reporting on myeloid cells.

The applications of an <sup>18</sup>F-labeled perfusion agent [<sup>18</sup>F fluorodeoxyglucose (<sup>18</sup>F-FDG) and <sup>18</sup>F-sodium fluoride (<sup>18</sup>F-NaF)] for PET have

## Cardiac research by PET

**Table 1.** Radiotracer characteristics and application of PET in cardiac Research

Researcher	Species	Radionuclide	Application
Daly [24]	C57BL/6 mice	[ <sup>13</sup> N]NH <sub>3</sub> and [ <sup>18</sup> F]FDG	Monitoring the development of cardiac allograft rejection
Hoff [16]	Rat	<sup>13</sup> NH <sub>3</sub> and [ <sup>18</sup> F]FDG	A potential diagnostic role of PET
Ueno [21]	Female 57BL/6 mice	Isotope copper-64	Predicting organ survival by reporting on myeloid cells
Srivatsava [17]	Patients	[ <sup>18</sup> F]FDG	The assessment of myocardial viability in patients with left ventricular dysfunction
Meeder [13]	Patients	[ <sup>13</sup> N]NH <sub>3</sub>	Exploring the pathophysiology of smoking-related coronary events
Gerber [25]	Patients	[ <sup>18</sup> F]FDG	Predicting recovery of global cardiac function
Siebelink [26]	Patients	[ <sup>13</sup> N]NH <sub>3</sub> and [ <sup>18</sup> F]FDG	The assessment of revascularization with suspicion of jeopardized myocardium
De Jong [27]	Patients	[(11)C]CGP 12177	Measurement of myocardial beta-adrenoceptor density
De Boer [28]	Patients	Tc-MIBI and [ <sup>18</sup> F]FDG	The assessment of myocardial viability

revealed details on the pathophysiology of cardiovascular diseases [22]. Some radiotracers have unique effects, such as F-labeled fluorodeoxyglucose ([F]FDG) reflects glucose flux and N-labeled ammonia ([N]NH<sub>3</sub>) stand for a bio-marker of blood flow [23].

The relevant characteristics of radiotracer, animal models compared with human disease are listed in **Table 1** and discussed below.

### *PET imaging to monitor the allograft rejection*

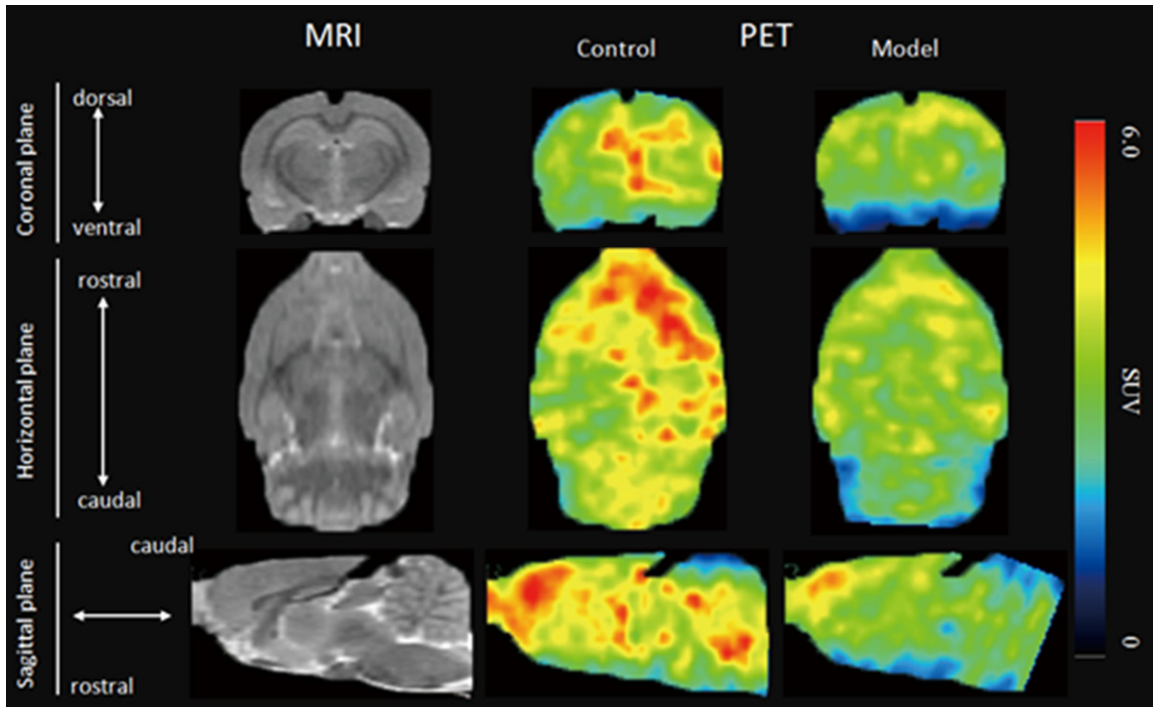
Owing to have the potential to be a specific, sensitive and quantitative diagnostic test, PET imaging in conjunction with radiotracers such as F-labeled fluorodeoxyglucose ([F]FDG) reflecting glucose flux and N-labeled ammonia ([N]NH<sub>3</sub>) reflecting blood flow, is increasingly used in clinical routine for transplant rejection detection [29, 30], yielding high diagnostic information, while providing valuable outcome in human transplant recipients [31]. Hoff [16] evaluated for the ability of positron-emitting tracers [<sup>13</sup>NH<sub>3</sub> and <sup>18</sup>F 2-fluoro 2-deoxyglucose (<sup>18</sup>F-FDG)] to detect acute allograft rejection after heterotopic cardiac transplantation in the rat with sham-operated controls, nonrejecting isografts, and rejecting allografts, and found that uptake of <sup>18</sup>F-FDG and <sup>13</sup>NH<sub>3</sub> in native hearts of animals from all experimental groups is not significantly different from that in sham-operated controls, suggesting that glucose may be a preferred metabolic substrate during rejection, which supports a humoral mechanism for substrate preference during transplant rejection and a potential diagnostic role for PET.

Daly [24] evaluated N-labeled ammonia ([N]NH<sub>3</sub>) reflecting myocardial perfusion and <sup>18</sup>F-labeled fluorodeoxyglucose ([<sup>18</sup>F]FDG) small

animal PET imaging in a well-established murine cardiac rejection model, and found that there was a significant increase in [F]FDG uptake in allografts from 14 d to 21 d, and [F]FDG uptake correlated with an increase in rejection grade within allografts between 14 d and 28 d after transplantation; whereas the uptake of [N]NH<sub>3</sub> was significantly lower relative to the native heart in allografts with chronic vasculopathy compared to isograft controls on 28 d, suggesting that PET imaging with [F]FDG can be used after transplantation to monitor the evolution of rejection, and decreased uptake of [N]NH<sub>3</sub> in rejecting allografts may be reflective of decreased myocardial blood flow. These data suggest that combined [F]FDG and [N]NH<sub>3</sub> PET imaging could contribute to unravel pathophysiological mechanisms underlying allograft rejection as a noninvasive, quantitative technique, and has potential application for serial monitoring of allograft rejection in human transplant recipients.

### *PET imaging to monitor the cerebral glucose metabolic change after cardiac ischemia/reperfusion*

There is a growing concern about heart-brain neural crosstalk. Understanding neural mechanisms could lead to a better comprehension of cerebral circuit structure and function after cardiac ischemia/reperfusion injury. We used PET imaging to monitor the cerebral glucose metabolic changes after cardiac ischemia/reperfusion (**Figure 1**). Surgical procedures of myocardial ischemia-reperfusion injury models were performed following previously described methods [32-35]. After reperfusion, approximate 500 ± 50 µCi 18-fluoro-6-deoxy-glucose (<sup>18</sup>F-FDG) was injected via the tail vein. After 1 h of <sup>18</sup>F-FDG uptake, rats were anesthetized with 2% isoflurane. Images were obtained with the



**Figure 1.** Alternations of glucose metabolism by small animal PET scanning. Representative images of  $^{18}\text{F}$ -FDG accumulation in the rats' brains of two groups (Control group and Model group). The images were displayed in three planes: coronal, horizontal, and sagittal planes.

whole body scanning pattern (5 min per scanning bed) by the Trans-PET BioCaliburn 700 system (Raycan Technology Co., Ltd, Suzhou, China). The PET images were reconstructed using the three-dimensional (3D) OSEM method with a voxel size of  $0.5 \times 0.5 \times 0.5 \text{ mm}^3$ . A volume-of-interest (VOI) analysis was conducted using the AMIDE software package (The Free Software Foundation Inc., Boston, Massachusetts, USA).

#### *PET imaging in the assessment of sympathetic re-innervation after heart transplantation*

Some reports show that structural sympathetic re-innervation of the transplanted heart can develop after cardiac transplantation [36-39], but the evidence can be difficult to diagnose. Schwaiblmair [40] investigated the influence of sympathetic re-innervation on cardiopulmonary exercise testing after orthotopic heart transplantation in 35 patients underwent PET, and found that sympathetic re-innervation enabled an increased peak oxygen uptake, suggesting that partial sympathetic reinnervation after cardiac transplantation is of functional significance. Schwaiger [41] studied possible

re-innervation of the human transplant after cardiac transplant by PET imaging approach in combination with catecholamine analogue [ $^{11}\text{C}$ ] hydroxyephedrine ([ $^{11}\text{C}$ ]HED), and found that there is the presence of sympathetic neuronal tissue in the terminals of transplanted human heart, which may reflect local sympathetic re-innervation. Bengel [42] described individual growth of sympathetic terminals late after cardiac transplantation by a longitudinal quantitative assessment, and found that sympathetic re-innervation was happened in the basal anterior region, apex, septal, and lateral wall, whereas inferior wall remained denervated; the largest reinnervated area surveyed in an individual was 66% of the left ventricle, suggesting that re-innervation remained regionally heterogeneous.

#### *PET imaging to predict recovery of global cardiac function*

The past decade has seen strong progress in understanding PET imaging accuracy for predicting recovery of cardiac function after revascularization [43-45]. Gerber [25] assessed the accuracy of PET to predict recovery of global

cardiac function after revascularization in 157 male patients with coronary artery disease, and found that the highest sensitivity (79%) and specificity (55%) predicted postoperative ejection fraction improvement by using  $^{18}\text{F}$ -FDG PET, suggesting that FDG positron emission tomography can predict improvement of cardiac function coronary patients with impaired ejection fraction. Srivatsava [17] prospectively studied 120 patients with left ventricular (LV) dysfunction who underwent  $^{99\text{m}}\text{Tc}$ -Sestamibi myocardial perfusion SPECT-CT and  $^{18}\text{F}$ -FDG cardiac PET-CT, and indicated that the change in LV impaired ejection after surgical management was statistically significant compared to medical management, and the assessment of myocardial viability was performed in patients who present after 12 h of acute myocardial infarction or with LV dysfunction due to ischemic heart disease to decide upon appropriate surgical management, suggest that there is an important role of PET-CT in assessment of myocardial viability in patients with LV dysfunction.

### *PET imaging to evaluate the cardiovascular effects of drugs and stimulation*

Within the last decade, PET imaging has translated from a mere research tool to the cardiovascular efficacy of drugs by myocardial perfusion imaging and flow quantification. Molecular imaging tools including PET are increasingly applied in the drug development process [46].

Ueno [21] imaged the effects of angiotensin-converting enzyme inhibitor (5 mg/kg enalapril) in mice with heart allografts, and found that enalapril significantly decreased macrophage-avid nanoparticle signal by using sensitive positron emission tomography-computed tomography (PET-CT) imaging, and reduced a number of myeloid cells in the graft, blood, and lymph nodes by histology and flow cytometry, suggesting that angiotensin-converting enzyme inhibitor significantly prolong allograft survival.

Spinal cord stimulation causes significant symptomatic improvement in many patients with refractory angina pectoris [37, 47-49], and the mechanism underlying this beneficial response is not fully known [50-53]. Hautvast [54] assessed the effect of spinal cord stimulation on myocardial blood flow by positron emission tomography in patients with refractory angina

pectoris, and found that after 6 weeks of stimulation, both frequency of daily anginal attacks and nitrogen consumption decreased, and the coefficient of variation of flow, representing flow heterogeneity, decreased after treatment, both at rest and after dipyridamole stress, suggesting that spinal cord stimulation is clinically effective due to homogenization of myocardial blood flow. Posma et al. [55] also reported a redistribution of myocardial flow during dual chamber pacing in a patient with non-obstructive hypertrophic cardiomyopathy by positron emission tomography, suggesting that early septal activation reduced septal fibre strain and blood flow and increased septal perfusion reserve.

### **Acknowledgements**

This work was supported in part by grants from the National Natural Science Foundation of China (No. 81670240, 81770283, 81072152) and the Clinical Medical Research Center of Peritoneal Cancer of Wuhan (No. 201506091-1020462) and the Natural Science Foundation of Hubei Province (No. 2015CFA027), the Research Foundation of Health and Family Planning Commission of Hubei Province (No. WJ2015MA010, WJ2017M249) and Medical innovation project in Fujian Province (No. 2017-CX-48).

### **Disclosure of conflict of interest**

None.

**Address correspondence to:** Dr. Mao-Hui Feng, Department of Gastrointestinal Surgery, Zhongnan Hospital, Wuhan University, No. 169 Donghu Road, Wuhan 430071, Hubei, PR China. E-mail: fengmh5690@163.com; Dr. Hong-Bing Xiang, Department of Anesthesiology and Pain Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, PR China. E-mail: xhbtj2004@163.com

### **References**

- [1] Li R, Wong GT, Wong TM, Zhang Y, Xia Z and Irwin MG. Intrathecal morphine preconditioning induces cardioprotection via activation of delta, kappa, and mu opioid receptors in rats. *Anesth Analg* 2009; 108: 23-29.
- [2] Wong GT, Yao L, Xia Z and Irwin MG. Intrathecal morphine remotely preconditions the heart via

## Cardiac research by PET

- a neural pathway. *J Cardiovasc Pharmacol* 2012; 60: 172-178.
- [3] Lu Y, Hu J, Zhang Y, Dong CS and Wong GT. Remote intrathecal morphine preconditioning confers cardioprotection via spinal cord nitric oxide/cyclic guanosine monophosphate/protein kinase G pathway. *J Surg Res* 2015; 193: 43-51.
- [4] Xu LJ, Liu TT, He ZG, Hong QX and Xiang HB. Hypothesis: CeM-RVLM circuits may be implicated in sudden unexpected death in epilepsy by melanocortinergic-sympathetic signaling. *Epilepsy Behav* 2015; 45: 124-127.
- [5] Foreman RD, Garrett KM and Blair RW. Mechanisms of cardiac pain. *Compr Physiol* 2015; 5: 929-960.
- [6] Santos SF, Rebelo S, Derkach VA and Safronov BV. Excitatory interneurons dominate sensory processing in the spinal substantia gelatinosa of rat. *J Physiol* 2007; 581: 241-254.
- [7] Franco-Cereceda A, Kallner G and Lundberg JM. Capsazepine-sensitive release of calcitonin gene-related peptide from C-fibre afferents in the guinea-pig heart by low pH and lactic acid. *Eur J Pharmacol* 1993; 238: 311-316.
- [8] Steagall RJ, Sipe AL, Williams CA, Joyner WL and Singh K. Substance P release in response to cardiac ischemia from rat thoracic spinal dorsal horn is mediated by TRPV1. *Neuroscience* 2012; 214: 106-119.
- [9] Pirich C and Schwaiger M. The clinical role of positron emission tomography in management of the cardiac patient. *Rev Port Cardiol* 2000; 19 Suppl 1: I89-100.
- [10] Elsinga PH, Doze P, van Waarde A, Pieterman RM, Blanksma PK, Willemsen AT and Vaalburg W. Imaging of beta-adrenoceptors in the human thorax using (S)-[(11)C]CGP12388 and positron emission tomography. *Eur J Pharmacol* 2001; 433: 173-176.
- [11] Meeder JG, Peels HO, Blanksma PK, Tan ES, Pruim J, van der Wall EE, Vaalburg W and Lie KI. Comparison between positron emission tomography myocardial perfusion imaging and intracoronary Doppler flow velocity measurements at rest and during cold pressor testing in angiographically normal coronary arteries in patients with one-vessel coronary artery disease. *Am J Cardiol* 1996; 78: 526-531.
- [12] Meeder JG, Blanksma PK, van der Wall EE, Willemsen AT, Pruim J, Anthonio RL, de Jong RM, Vaalburg W and Lie KI. Coronary vasomotion in patients with syndrome X: evaluation with positron emission tomography and parametric myocardial perfusion imaging. *Eur J Nucl Med* 1997; 24: 530-537.
- [13] Meeder JG, Blanksma PK, van der Wall EE, Anthonio RL, Willemsen AT, Pruim J, Vaalburg W and Lie KI. Long-term cigarette smoking is associated with increased myocardial perfusion heterogeneity assessed by positron emission tomography. *Eur J Nucl Med* 1996; 23: 1442-1447.
- [14] Schindler TH. Positron-emitting myocardial blood flow tracers and clinical potential. *Prog Cardiovasc Dis* 2015; 57: 588-606.
- [15] Bergstrom M, Awad R, Estrada S, Malman J, Lu L, Lendvai G, Bergstrom-Pettermann E and Langstrom B. Autoradiography with positron emitting isotopes in positron emission tomography tracer discovery. *Mol Imaging Biol* 2003; 5: 390-396.
- [16] Hoff SJ, Stewart JR, Frist WH, Kessler RM, Sandler MP, Atkinson JB, Votaw J, Carey JA, Ansari MS and Merrill WH. Noninvasive detection of heart transplant rejection with positron emission scintigraphy. *Ann Thorac Surg* 1992; 53: 572-577.
- [17] Srivatsava MK, Indirani M, Sathyamurthy I, Sengottuvelu G, Jain AS and Shelley S. Role of PET-CT in the assessment of myocardial viability in patients with left ventricular dysfunction. *Indian Heart J* 2016; 68: 693-699.
- [18] Reddan MC and Wager TD. Modeling pain using fMRI: from regions to biomarkers. *Neurosci Bull* 2018; 34: 208-215.
- [19] Christen T, Nahrendorf M, Wildgruber M, Swirski FK, Aikawa E, Waterman P, Shimizu K, Weissleder R and Libby P. Molecular imaging of innate immune cell function in transplant rejection. *Circulation* 2009; 119: 1925-1932.
- [20] Ye Q, Wu YL, Foley LM, Hitchens TK, Eytan DF, Shirwan H and Ho C. Longitudinal tracking of recipient macrophages in a rat chronic cardiac allograft rejection model with noninvasive magnetic resonance imaging using micrometer-sized paramagnetic iron oxide particles. *Circulation* 2008; 118: 149-156.
- [21] Ueno T, Dutta P, Keliher E, Leuschner F, Majumdar M, Marinelli B, Iwamoto Y, Figueiredo JL, Christen T, Swirski FK, Libby P, Weissleder R and Nahrendorf M. Nanoparticle PET-CT detects rejection and immunomodulation in cardiac allografts. *Circ Cardiovasc Imaging* 2013; 6: 568-573.
- [22] Lee WW. Recent advances in nuclear cardiology. *Nucl Med Mol Imaging* 2016; 50: 196-206.
- [23] Blanksma PK and Pruim J. Positron emission tomography: measurement of myocardial perfusion using (13)N-labeled ammonia and (15)O-labeled water. *Methods* 2002; 27: 226-227.
- [24] Daly KP, Dearling JL, Seto T, Dunning P, Fahey F, Packard AB and Briscoe DM. Use of [18F] FDG positron emission tomography to monitor the development of cardiac allograft rejection. *Transplantation* 2015; 99: e132-139.
- [25] Gerber BL, Ordoubadi FF, Wijns W, Vanoverschelde JL, Knuuti MJ, Janier M, Melon P,

- Blanksma PK, Bol A, Bax JJ, Melin JA and Camici PG. Positron emission tomography using (18)F-fluoro-deoxyglucose and euglycaemic hyperinsulinaemic glucose clamp: optimal criteria for the prediction of recovery of post-ischaemic left ventricular dysfunction. Results from the European community concerted action multicenter study on use of (18)F-fluoro-deoxyglucose positron emission tomography for the detection of myocardial viability. *Eur Heart J* 2001; 22: 1691-1701.
- [26] Siebelink HM, Blanksma PK, Crijns HJ, Bax JJ, van Boven AJ, Kingma T, Piers DA, Pruijm J, Jager PL, Vaalburg W and van der Wall EE. No difference in cardiac event-free survival between positron emission tomography-guided and single-photon emission computed tomography-guided patient management: a prospective, randomized comparison of patients with suspicion of jeopardized myocardium. *J Am Coll Cardiol* 2001; 37: 81-88.
- [27] de Jong RM, Blanksma PK, van Waarde A and van Veldhuisen DJ. Measurement of myocardial beta-adrenoceptor density in clinical studies: a role for positron emission tomography? *Eur J Nucl Med Mol Imaging* 2002; 29: 88-97.
- [28] De Boer J, Slart RH, Blanksma PK, Willemsen AT, Jager PL, Paans AM, Vaalburg W and Piers DA. Comparison of 99mTc-sestamibi-18F-fluorodeoxyglucose dual isotope simultaneous acquisition and rest-stress 99mTc-sestamibi single photon emission computed tomography for the assessment of myocardial viability. *Nucl Med Commun* 2003; 24: 251-257.
- [29] Kashiyama N, Miyagawa S, Fukushima S, Kawamura T, Kawamura A, Yoshida S, Harada A, Watabe T, Kanai Y, Toda K, Hatazawa J and Sawa Y. Development of PET imaging to visualize activated macrophages accumulated in the transplanted iPSc-derived cardiac myocytes of allogeneic origin for detecting the immune rejection of allogeneic cell transplants in mice. *PLoS One* 2016; 11: e0165748.
- [30] Wareham NE, Lundgren JD, Da Cunha-Bang C, Gustafsson F, Iversen M, Johannesen HH, Kjaer A, Rasmussen A, Sengelov H, Sorensen SS and Fischer BM. The clinical utility of FDG PET/CT among solid organ transplant recipients suspected of malignancy or infection. *Eur J Nucl Med Mol Imaging* 2017; 44: 421-431.
- [31] Chen Y, Zhang L, Liu J, Zhang P, Chen X and Xie M. Molecular imaging of acute cardiac transplant rejection: animal experiments and prospects. *Transplantation* 2017; 101: 1977-1986.
- [32] Murry CE, Jennings RB and Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; 74: 1124-1136.
- [33] Huang CH, Lai CC, Yang AH and Chiang SC. Myocardial preconditioning reduces kidney injury and apoptosis induced by myocardial ischemia and reperfusion. *Eur J Cardiothorac Surg* 2015; 48: 382-391.
- [34] Li ZX, Lin Q, He ZG, Wang Q, Chen YL, Feng MH, Li SY and Xiang HB. Altered myocardial gene expression profiling in the ischemic tissues at different time points after cardiac ischemia/reperfusion in rats. *Oncotarget* 2018; 9.
- [35] Wang Q, Li ZX, Liu BW, He ZG, Liu C, Chen M, Liu SG, Wu WZ and Xiang HB. Altered expression of differential gene and lncRNA in the lower thoracic spinal cord on different time courses of experimental obstructive jaundice model accompanied with altered peripheral nociception in rats. *Oncotarget* 2017; 8: 106098-106112.
- [36] Buendia-Fuentes F, Almenar L, Ruiz C, Vercher JL, Sanchez-Lazaro I, Martinez-Dolz L, Navarro J, Bello P and Salvador A. Sympathetic reinnervation 1 year after heart transplantation, assessed using iodine-123 metaiodobenzylguanidine imaging. *Transplant Proc* 2011; 43: 2247-2248.
- [37] Singh H, Merry AF, Ruygrok P and Ruttley A. Treatment of recurrent chest pain in a heart transplant recipient using spinal cord stimulation. *Anaesth Intensive Care* 2008; 36: 242-244.
- [38] De Marco T, Dae M, Yuen-Green MS, Kumar S, Sudhir K, Keith F, Amidon TM, Rifkin C, Klinski C, Lau D, et al. Iodine-123 metaiodobenzylguanidine scintigraphic assessment of the transplanted human heart: evidence for late reinnervation. *J Am Coll Cardiol* 1995; 25: 927-931.
- [39] Kaye DM, Esler M, Kingwell B, McPherson G, Esmore D and Jennings G. Functional and neurochemical evidence for partial cardiac sympathetic reinnervation after cardiac transplantation in humans. *Circulation* 1993; 88: 1110-1118.
- [40] Schwaiblmair M, von Scheidt W, Uberfuhr P, Ziegler S, Schwaiger M, Reichart B and Vogelmeier C. Functional significance of cardiac reinnervation in heart transplant recipients. *J Heart Lung Transplant* 1999; 18: 838-845.
- [41] Schwaiger M, Hutchins GD, Kalff V, Rosenspire K, Haka MS, Mallette S, Deeb GM, Abrams GD and Wieland D. Evidence for regional catecholamine uptake and storage sites in the transplanted human heart by positron emission tomography. *J Clin Invest* 1991; 87: 1681-1690.
- [42] Bengel FM, Ueberfuhr P, Ziegler SI, Nekolla S, Reichart B and Schwaiger M. Serial assessment of sympathetic reinnervation after orthotopic heart transplantation. A longitudinal study using PET and C-11 hydroxyephedrine. *Circulation* 1999; 99: 1866-1871.
- [43] Raja S, Mittal BR, Santhosh S, Bhattacharya A and Rohit MK. Comparison of LVEF assessed

## Cardiac research by PET

- by 2D echocardiography, gated blood pool SPECT, <sup>99m</sup>Tc tetrofosmin gated SPECT, and <sup>18</sup>F-FDG gated PET with ERNV in patients with CAD and severe LV dysfunction. *Nucl Med Commun* 2014; 35: 1156-1161.
- [44] Uebleis C, Hellweger S, Laubender RP, Becker A, Sohn HY, Lehner S, Haug A, Bartenstein P, Cumming P, Van Krieking SD, Slomka PJ and Hacker M. The amount of dysfunctional but viable myocardium predicts long-term survival in patients with ischemic cardiomyopathy and left ventricular dysfunction. *Int J Cardiovasc Imaging* 2013; 29: 1645-1653.
- [45] Raja S, Singh B, Rohit MK, Manohar K, Kashyap R, Bhattacharya A and Mittal BR. Comparison of nitrate augmented Tc-99m tetrofosmin gated SPECT imaging with FDG PET imaging for the assessment of myocardial viability in patients with severe left ventricular dysfunction. *J Nucl Cardiol* 2012; 19: 1176-1181.
- [46] Fernandes E, Barbosa Z, Clemente G, Alves F and Abrunhosa AJ. Positron emitting tracers in pre-clinical drug development. *Curr Radiopharm* 2012; 5: 90-98.
- [47] Lopshire JC, Zhou X, Dusa C, Ueyama T, Rosenberger J, Courtney N, Ujhelyi M, Mullen T, Das M and Zipes DP. Spinal cord stimulation improves ventricular function and reduces ventricular arrhythmias in a canine postinfarction heart failure model. *Circulation* 2009; 120: 286-294.
- [48] Issa ZF, Zhou X, Ujhelyi MR, Rosenberger J, Bhakta D, Groh WJ, Miller JM and Zipes DP. Thoracic spinal cord stimulation reduces the risk of ischemic ventricular arrhythmias in a postinfarction heart failure canine model. *Circulation* 2005; 111: 3217-3220.
- [49] Mannheimer C, Eliasson T, Augustinsson LE, Blomstrand C, Emanuelsson H, Larsson S, Norrsell H and Hjalmarsson A. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY study. *Circulation* 1998; 97: 1157-1163.
- [50] Ding X, Ardell JL, Hua F, McAuley RJ, Sutherly K, Daniel JJ and Williams CA. Modulation of cardiac ischemia-sensitive afferent neuron signaling by preemptive C2 spinal cord stimulation: effect on substance P release from rat spinal cord. *Am J Physiol Regul Integr Comp Physiol* 2008; 294: R93-101.
- [51] Hua F, Ardell JL and Williams CA. Left vagal stimulation induces dynorphin release and suppresses substance P release from the rat thoracic spinal cord during cardiac ischemia. *Am J Physiol Regul Integr Comp Physiol* 2004; 287: R1468-1477.
- [52] Gibbons DD, Southerland EM, Hoover DB, Beaumont E, Armour JA and Ardell JL. Neuro-modulation targets intrinsic cardiac neurons to attenuate neuronally mediated atrial arrhythmias. *Am J Physiol Regul Integr Comp Physiol* 2012; 302: R357-364.
- [53] Ardell JL, Cardinal R, Beaumont E, Vermeulen M, Smith FM and Andrew Armour J. Chronic spinal cord stimulation modifies intrinsic cardiac synaptic efficacy in the suppression of atrial fibrillation. *Auton Neurosci* 2014; 186: 38-44.
- [54] Hautvast RW, Blanksma PK, DeJongste MJ, Pruijm J, van der Wall EE, Vaalburg W and Lie KI. Effect of spinal cord stimulation on myocardial blood flow assessed by positron emission tomography in patients with refractory angina pectoris. *Am J Cardiol* 1996; 77: 462-467.
- [55] Pasma JL, Blanksma PK and van der Wall EE. Redistribution of myocardial perfusion during permanent dual chamber pacing in symptomatic non-obstructive hypertrophic cardiomyopathy: a quantitative positron emission tomography study. *Heart* 1996; 75: 522-524.