

Alterations of cell-mediated immunity following cardiac operations: clinical implications and open questions

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Summary

Cardiac surgery with cardiopulmonary bypass (CPB) is known to induce an immune response whose nature has been increasingly elucidated during the recent decade. Clinically, patients usually show two to three of the four symptoms, which define the so-called systemic inflammatory response syndrome (SIRS). In addition, all parameters of the innate, nonspecific immune system, e.g., polymorphonuclear cells, elastase, and complement, are activated. This also applies to the proinflammatory mediators interleukin (IL)-1 β , -6, and -8, and tumor necrosis factor (TNF)- α . Within the adaptive, specific immune system, a decrease of T lymphocytes and T helper (TH) cells is observed, whereas suppressor/cytotoxic T cells and B cells appear to be nearly unaffected.

Cytokine measurements provide more detailed information: IL-2 and IL-12, which are important for the activation of the type-1 TH-cell (TH1)-mediated immune response, are depressed following cardiac operation. In contrast, IL-10 and transforming growth factor- β essential to TH2-mediated humoral or anti-inflammatory immune response, are upregulated. *In vivo* tests, e.g., delayed type hypersensitivity skin reaction and tetanus antibody production, confirm the polarization of the adaptive immune response towards the TH2 pathway.

However, all these alterations usually do not result in clinical adverse events. Therefore, more information is needed about the immune response of patients at high preoperative risk or with serious perioperative complications to find out whether clinically relevant events are correlated to alterations of immune response. For this purpose, more readily available, standardized methods for immunologic monitoring appear highly desirable.

References

1. Westaby S: Complement and the damaging effect of cardiopulmonary bypass. *Thorax* 38:321-325, 1983.
2. Brett SJ, Quinlan GJ, Mitchell J, Pepper JR, Evans TW: Production of nitric oxide during surgery involving cardiopulmonary bypass. *Crit Care Med* 26: 272-278, 1998.

3. Asimakopoulos G, Kohn A, Stefanou DC, Haskard DO, Landis RC, Taylor KM: Leukocyte integrin expression in patients undergoing cardiopulmonary bypass. *Ann Thorac Surg* 69:1192-1197, 2000.
4. Chello M, Mastroroberto P, Romano R, Ascione R, Pantaleo D, de Amicis V: Complement and neutrophil activation during cardiopulmonary bypass: a randomized comparison of hypothermic and normothermic circulation. *Eur J Cardiothorac Surg* 11:162-168, 1997.
5. Shimono T, Nose Y, Yada I, Kanamori Y, Makino S, Kusagawa H, Sato T, Kusagawa M: Is it true that cardiac operations with cardiopulmonary bypass impair the reticuloendothelial System? *Ann Thorac Surg* 58:1059-1063, 1994.
6. Markewitz A, Rudolph G, Rothenburger M, Kuhlmann WD: Impact of leukocyte activation on the innate immune System following cardiac surgery. *Shock* 7:A107, 1997.
7. Det'raigne JO, Pincemail J, Larbuisson R, Blaffard F, Limet R: Cytokine release and neutrophil activation are not prevented by heparin-coated circuits and aprotinin administration. *Ann Thorac Surg* 69:1084-1091, 2000.
8. Birdi I, Caputo M, Underwood M, Bryan AJ, Angelini GD: The effects of cardiopulmonary bypass temperature on inflammatory response following cardiopulmonary bypass. *Eur J Cardiothorac Surg* 16:540-545, 1999.
9. Misoph M, Babin-Ebell J, Schwender S, Grossmann R, Keller F, Eiert O: Response of the cellular immune System to cardiopulmonary bypass *in vivo*. *Thorac Cardiovasc Surg* 45:217-223, 1997.
10. Markewitz A, Faist E, Weinhold C, Lang S, Endres S, Hühner L, et al.: Alterations of cell-mediated immune response following cardiac surgery. *Eur J Cardiothorac Surg* 7:193-199, 1993.
11. Diegeler A, Tärnok A, Rauch T, Haberer D, Falk V, Battelini R, et al.: Changes of leukocyte subsets in coronary artery bypass surgery: cardiopulmonary bypass versus off-pump techniques. *Thorac Cardiovasc Surg* 46:327-332, 1998.
12. Markewitz A, Faist E, Lang S, Hühner L, Weinhold C, Reichart B: An imbalance in T-helper cell subsets alters immune response after cardiac surgery. *Eur J Cardiothorac Surg* 10:61-67, 1996.
13. Markewitz A, Faist E, Lang S, Endres S, Fuchs D, Reichart B: Successful restoration of cell-mediated immune response after cardiopulmonary bypass by immunomodulation. *J Thorac Cardiovasc Surg* 105:15-24, 1993.
14. Casey LC: Role of cytokines in the pathogenesis of cardiopulmonary-induced multi-system organ failure. *Ann Thorac Surg* 56:592-596, 1993.
15. Hayashida N, Tomoeda H, Oda T, et al.: Inhibitory effect of milrinone on cytokine production after cardiopulmonary bypass. *Ann Thorac Surg* 68:1661-1667, 1999.
16. Wan S, Marchant A, DeSmet JM, et al.: Human cytokine responses to cardiac transplantation and coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 111: 469-477, 1996.
17. Wan S, DeSmet JM, Barvais L, Goldstein M, Vincent JL, LeClerc JL: Myocardium is a major source of proinflammatory cytokines in patients undergoing cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 112:806-811, 1996.
18. Grünnefelder J, Zünd G, Schoeberlein A, et al.: Modified ultrafiltration lowers adhesion molecule and cytokine levels after cardiopulmonary bypass without clinical relevance in adults. *Eur J Cardiothorac Surg* 17:77-83, 2000.

19. Hang F, Feyrer R, Mahmoud FO, Blum U, v.d.Emde J: Reducing the postpump syndrome by using heparin-coated circuits, steroids, or aprotinin. *Thorac Cardiovasc Surg* 47:111-118, 1999.
20. Horton SB, Butt WW, Mullaly RJ, et al.: IL-6 and IL-8 levels after cardiopulmonary bypass are not affected by surface coating. *Ann Thorac Surg* 68:1751-1755, 1999.
21. Liebold A, Keyl C, Birnbaum DE: The heart produces but the lungs consume proinflammatory cytokines following cardiopulmonary bypass. *Eur J Cardiothorac Surg* 15:340-345, 1999.
22. Sablotzki A, Dehne MG, Mann V, et al.: Plasma levels of selectins and interleukins in cardiovascular surgery using cardiopulmonary bypass. *Thorac Cardiovasc Surg* 47:26-31. 1999.
23. Hisatomi K, Isomura T, Kawara T, et al.: Changes in lymphocyte subsets, mitogen responsiveness, and interleukin-2 production after cardiac operations. *J Thorac Cardiovasc Surg* 98:580-591, 1989.
24. Hisatomi K, Kobayashi A, Moriyama Y, Shimokawa S, Toyohira H, Taira A: Combined suppressive effect of cardiopulmonary bypass and aging on cell-mediated immunity. *J Thorac Cardiovasc Surg* 114:140-141. 1997.
25. Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD: Inflammatory response after coronary revascularization with or without cardiopulmonary bypass. *Ann Thorac Surg* 69:1198-1204, 2000.
26. Struber M, Cremer JT, Gohrbandt B, Hagl C, Jankowski M, Volker B, Ruckoldt H, Martin M, Haverich A: Human cytokine response to coronary artery bypass grafting with and without cardiopulmonary bypass. *Ann Thorac Surg* 68:1330-1335, 1999.
27. Harig F, Cesnjevar R, Mahmoud FO, v.d.Emde J: Perioperative factors influencing interleukin-10 release under cardiopulmonary bypass. *Thorac Cardiovasc Surg* 47: 361-368, 1999.
28. Hill GE, Diego RP, Stammers AH, Huffmann SM; Pohorecki R: Aprotinin enhances the endogenous release of interleukin-10 after cardiac operations. *Ann Thorac Surg* 65:66-69, 1998.
29. Sablotzki A, Welters I, Lehmann N, Menges T, Gorchach G, Dehne M, Hempelmann G: Plasma levels of immunoinhibitory cytokines interleukin-10 and transforming growth factor- β in patients undergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg* 11:763-768, 1997.
30. Delves PJ, Roitt IM: The immune system: first of two parts. *N Engl J Med* 343:37-19, 2000.
31. <http://www.keratin.com/am/amindex/shtmlm>
32. <http://www.copewithcytokines.de>
33. [http://www.cat.cc.md.us/courses/bio 14 l/lecguide/unit3](http://www.cat.cc.md.us/courses/bio%2014/lecguide/unit3)
34. <http://www.path.cam.ac.uk/immuno/part1>
35. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL: Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 136:2348-2357, 1986.
36. Oberholzer A, Oberholzer C, Moldawer LL: Cytokine signaling: regulation of the immune response in normal and critically ill states. *Crit Care Med* 28(Suppl):N3-N12, 2000.

37. Power CA: Factors that influence T helper cell response to infection. *Curr Opin Infect Dis* 13:209-213, 2000.
38. Wan S, Izzat MB, Lee TW, Wan IYP, Tang NLS, Yim APC: Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. *Ann Thorac Surg* 68:52-57, 1999.
39. Richter JA, Meisner H, Tassani P, Barankay A, Dietrich W, Braun SL: Drew-Anderson technique attenuates systemic inflammatory response syndrome and improves respiratory function after coronary artery bypass grafting. *Ann Thorac Surg* 69:77-83, 1999.
40. Kotani N, Hashimoto H, Sessler DI, Muraoka M, Wang JS, O'Connor MF, Matsuki A: Cardiopulmonary bypass produces greater pulmonary than systemic proinflammatory cytokines. *Anaest Anaig* 90:1039-1045, 2000.
41. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: ACCP/SCCM consensus Conference: Definition for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 20:864-874, 1992.
42. Bone RC: Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med* 24:1125-1128, 1996.
43. Niebauer J, Volk HD, Kemp M, Dominguez M, Schumann RR, Rauchhaus M, Poole-Wilson PA, Coats AJ, Anker SD: Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet* 353:1838-1842, 1999.
44. Ahmed NA, McGill S, Yee J, Hu F, Michel RP, Christou NV: Mechanisms for the diminished neutrophil exudation to secondary inflammatory Sites in infected patients with a systemic inflammatory response. *Crit Care Med* 27:2459-2468, 1999.
45. Ankersmit HJ, Tugulea S, Spanier T, Weinberg AD, Artrip JH, Burke EM, Flannery M, Mancini D, Rose EA, Edwards NM, Oz MC, Itescu S: Activation-induced T-cell death and immune dysfunction after Implantation of left-ventricular assist device. *Lancet* 354:550-555, 1999.
46. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R: European System for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 16:9-13, 1999.
47. Kuhn C, Muller-Werdan U, Schmitt DV, Lange H, Pilz G, Kreuzer E, Mohr FW, Zerkowski HR, Werdan K: Improved outcome of APACHE II score-defined escalating systemic inflammatory response syndrome in patients post cardiac surgery in 1996 compared to 1998-1990: the ESSICS-study pilot project. *Eur J Cardiothorac Surg* 17:30-37, 2000.
48. Deng MC, Dasch B, Erren M, Müllhoff T, Scheid HH: Impact of left ventricular dysfunction on cytokines, hemodynamics, and outcome in bypass grafting. *Ann Thorac Surg* 62:184-190, 1996.
49. Cremer J, Martin M, Redl H, Bahrami S, Abraham C, Graeter T, Haverictl A, Schlag G, Borst HG: Systemic inflammatory response syndrome after cardiac operations. *Ann Thorac Surg* 61:1714-1720, 1996.
50. Koller-Strametz J, Pacher R, Frey B, Kos T, Woloszczuk W, Stanek B: Circulating tumor necrosis factor- α levels in chronic heart failure: relation to its soluble receptor II, interleukin-6, and neurohumoral variables. *J Heart Lung Transplant* 17:356-362, 1998.

51. Orus J, Roig E, Perez-Villa F, Pare C, Azqueta M, Fileila X, Heras M, Sanz G: Prognostic value of serum cytokines in patients with congestive heart failure. *J Heart Lung Transplant* 19:419-425, 2000.
52. Delogu G, Famularo G, Atnati F, Signore L, Antonucci A, Trinchieri V, Di Marzio L, Cifone MG: Ceramide concentrations in septic patients: a possible marker of multiple organ dysfunction syndrome. *Crit Care Med* 27:2413-2417, 1999.
53. Papathanassoglou EDE, Moynihan JA, Ackerman MH: Does programmed cell death (apoptosis) play a role in the development of multiple organ dysfunction in critically ill patients? A review and a theoretical framework. *Crit Care Med* 28:537-549, 2000.
54. Kox WJ, Volk T, Kox SN, Volk HD: Immunomodulatory therapy in sepsis. *Intensive Care Med* 26:S124-S128, 2000.
55. Christou NV, Meakins JL, Gordon J, Yee J, Hassan-Zahraee M, Nohr CW, Shizgal HM, MacLean LD: The delayed hypersensitivity response and host resistance in surgical patients: 20 years later. *Ann Surg* 222:534-548, 1995.
56. Markewitz A, Rothenburger M, Rudolph G, Kuhlmann WD: Humoral immune response following cardiac surgery: specific or nonspecific activation? *Shock* 7:A105, 1997.
57. Godin PJ, Buchman TG: Uncoupling of biological oscillators: a complimentary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. *Crit Care Med* 24:1107-1116, 1996.
58. Seely AJE, Christou NV: Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear Systems. *Crit Care Med* 28:2193-2200, 2000.