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Lampiran 1: Lembar Bimbingan

CATATAN BIMBINGAN SKRIPSI

Nama : Madaniawati Nurul Fitri

NIM : AK.1.16.034

Judul Skripsi : Pengaruh *Passsive Legs Raising* Terhadap Responsivitas Cairan pada Klien Syok Sepsis

Pembimbing Utama : Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

Pembimbing Pendamping : Sumbara,S.Kep.,Ners.,M.Kep

No	Hari /Tanggal	Catatan Pembimbing	Paraf Pembimbing
1.	Senin 02 Maret 2020	1. Kontrak waktu bimbingan. 2. Timeline. 3. Aturan main. 4. Menentukan tema penelitian. 5. Mencari 10-15 jurnal.	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
2.	Sabtu 14 Maret 2020	1. Bimbingan menentukan tema dan judul penelitian. 2. Buat BAB I.	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
3.	Rabu 15 April 2020	1. Bimbingan BAB I. 2. Lengkapi Bab II dan III. 3. Perbaiki penulisan dan ikuti rekomendasi.	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
4.	Minggu 26 April 2020	1. Bimbingan skripsi Revisi BAB I. 2. Bimbingan BAB II dan BAB III. 3. BAB I terlalu banyak teori, jika tidak ada studi lapangan kosongkan untuk tema studi lapangannya. 4. Teori di BAB I bisa dipindah ke BAB II.	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

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Nama : Madaniawati Nurul Fitri

NIM : AK.1.16.034

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Pembimbing Utama : Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

Pembimbing Pendamping : Sumbara,S.Kep.,Ners.,M.Kep

No	Hari /Tanggal	Catatan Pembimbing	Paraf Pembimbing
5.	Senin 11 Mei 2020	1. Persiapkan Daftar Sidang UP 2. ACC daftar sidang UP	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
6.	Selasa 19 Mei 2020	Sidang SUP	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
7.	Kamis 14 Mei 2020	1. Tinggal *finishing*. 2. Segera daftar sidang UP. 3. Langsung daftar perbaiki bahan-bahan yang sudah diperbaiki itu yang dipakai untuk sidang.	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
8.	Jum'at 10 Juli 2020	1. Bahan kajiannya belum dilengkapi. 2. Lengkapi hasil analisis dan kajiannya. 3. Buat BAB I -V lengkap gunakan Bahasa hasil.	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

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CATATAN BIMBINGAN SKRIPSI

Nama : Madaniawati Nurul Fitri

NIM : AK.1.16.034

Judul Skripsi : Pengaruh *Passsive Legs Raising* Terhadap Responsivitas Cairan pada Klien Syok Sepsis

Pembimbing Utama : Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

Pembimbing Pendamping : Sumbara,S.Kep.,Ners.,M.Kep

No	Hari /Tanggal	Catatan Pembimbing	Paraf Pembimbing
9.	Jum'at 07 Agustus 2020	1. Lihat panduan penulisan daftar isi. Spasi 1. 2. Jelaskan teknik dan bagaimana caranya penggunaan etika penelitian. 3. Waktu penelitian diubah jadi sampai Agustus. 4. Kelebihan dan kelemahan jurnal dibahas dalam analisis sesuai pendapat anda di pembahasna bukan berdasarkan teori tapi analisis anda buat nanti ya disimpan di pembahasan.	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
10.	Jum'at 07 Agustus 2020	1. Urutan pembahasan : 1. Hasil penelitian dibahas intinya, 2. Jelaskan teori teori yang mendukung adakan teori yang tidak mendukung paparkan, 3. jelaskan temuan di lahan penelitian 4. Jelaskan hambatan yang terjadi , 5. buat analisis knp hal itu terjadi dan jelaskan alasan2nya, 6. buat kajiannya dan analisis knp hasilnya bisa demikian lalu buat jelaskan mekanisme kerjanya atau tata caranya , 7. Jelaskan pendapat peneliti, 8. buat rekomendasi berdasarkan temuan dan pembahasan. Terapkan kesemua 2. Simpulan : Inti saja menjawab tujuan umum dan khusus apa jawabannya tidak usah mengulang pembahasna cukup isi utama nya apa saja. 3. Saran: Munculkan bahasannya di pembahasan,	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

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Nama : Madaniawati Nurul Fitri

NIM : AK.1.16.034

Judul Skripsi : Pengaruh *Passsive Legs Raising* Terhadap Responsivitas Cairan pada Klien Syok Sepsis

Pembimbing Utama : Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

Pembimbing Pendamping : Sumbara,S.Kep.,Ners.,M.Kep

No	Hari /Tanggal	Catatan Pembimbing	Paraf Pembimbing
11.	Minggu 23 Agustus 2020	1. Abstrak : Berapa banyak jurnal dapat dimana-mananya. 2. Daftar Pustaka : Perbaiki penulisan daftar pustaka sesuaikan dengan panduan, Perhatikan spasi, Tahun dibuat dalam kurung atau tidak,Penulis yang sama dengan judul yag sama pakai yg paling update,Penulis yang sama beda topik maka ditulis garis di penulis saat penulisan ke dua, Cek ricek dengan isi apakah sesuai isi daftar Pustaka dengan yg digunakan di bab 1 s.d 5, Link website dilengkapi bila diambil dari website Penulisan link harus benar klo link benar secara otomatis dia akan berwarna biru dan bisa langsung diakses bila diklik Perbaiki seluruhnya cek ricek semua 3. Perbaiki, Persiapkan daftar sidang	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
12.	Kamis 27 Agustus 2020	1. Acc daftar sidang akhir.	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

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Nama : Madaniawati Nurul Fitri

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Pembimbing Pendamping : Sumbara,S.Kep.,Ners.,M.Kep

No	Hari /Tanggal	Catatan Pembimbing	Paraf Pembimbing
13.	Sabtu 29 Agustus 2020	Sidang Akhir	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep
14.	Jum'at 11 September 2020	1. Evaluasi Post Sidang Akhir 2. ACC draft Skripsi	Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

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CATATAN BIMBINGAN SKRIPSI

Nama : Madaniawati Nurul Fitri

NIM : AK.1.16.034

Judul Skripsi : Pengaruh *Passsive Legs Raising* Terhadap Responsivitas Cairan pada Klien Syok Sepsis

Pembimbing Utama : Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

Pembimbing Pendamping : Sumbara,S.Kep.,Ners.,M.Kep

No	Hari /Tanggal	Catatan Pembimbing	Paraf Pembimbing
1	Jum'at 31 Januari 2020	1. Kontrak bimbingan, menentukan deadline. 2. Buat folder yang berisi cover sampai lampiran. 3. Cari grand teori untuk penelitiannya. 4. Kerangka piker dibuat dari kata-kata sendiri. 5. Instrument pastikan baku. 6. Buat isi dari cover hingga lampiran. 7. Gunakan numerikal semuanya.	Sumbara,S.Kep.,Ners.,M.Kep
2	Kamis 23 April 2020	1. Bimbingan BAB I, II. III. 2. Perbaiki penulisan. 3. Persiapan daftar UP.	Sumbara,S.Kep.,Ners.,M.Kep
3	Kamis 30 April 2020	1. Bimbingan Bab I, II, III. 2. Etika penelitian gunakan seperti plagiarism, dll. 3. Masukan hasil jurnal di BAB I. 4. Persiapkan nomor-nomor jurnal yang akan dianalisis nanti. 5. Awal kalimat tidak boleh singkatan. 6. Penulisan dirapihkan lagi terutama ketukannya.	Sumbara,S.Kep.,Ners.,M.Kep

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Pembimbing Utama : Nur Intan Hayati H.K.,S.Kep.,Ners.,M.Kep

Pembimbing Pendamping : Sumbara,S.Kep.,Ners.,M.Kep

No	Hari /Tanggal	Catatan Pembimbing	Paraf Pembimbing
4.	Selasa 05 Mei 2020	1. Manfaat penelitian ditambahkan lagi. 2. Metodologi penelitian diubah menjadi metode penelitian. 3. Sambel disebutkan jumlahnya dan dicantumkan nomor ISSN/ISBN atau DOI nya. 4. Ganti penomoran alfabetis menjadi numerikal.	Sumbara,S.Kep.,Ners.,M.Kep
5.	Rabu 13 Mei 2020	1. Acc daftar sidang UP. 2. Kirimkan draf proposal lengkap.	Sumbara,S.Kep.,Ners.,M.Kep
6.	Selasa 19 Mei 2020	Sidang SUP	Sumbara,S.Kep.,Ners.,M.Kep
7.	Minggu 28 Juli 2020	1. Evaluasi UP 2. Tambahkan buku panduan skripsi di Daftar Pustaka. 3. Coba pencarian jurnal dengan kata *Passive Legs Raising* diubah menjadi Bahasa Indonesia untuk mendapat jurnal Bahasa Indonesia. 4. Apabila di awal penomoran sudah menggunakan kurung tutup, maka penomoran dibawahnya gunakan kurung tutup jangan alfabetis.	Sumbara,S.Kep.,Ners.,M.Kep

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NIM : AK.1.16.034

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Pembimbing Pendamping : Sumbara,S.Kep.,Ners.,M.Kep

No	Hari /Tanggal	Catatan Pembimbing	Paraf Pembimbing
8.	Rabu 18 Agustus 2020	1. Simpulan harus menjawab tujuan umum dan khusus. 2. Penulisan kata skripsi diubah menjadi literature review. 3. Tabel terbuka apabila menggunakan lebih dari 1 halaman, menggunakan penomoran untuk keterangan. 4. Saran dan manfaat disesuaikan. 5. Tambahkan nomor jurnal dibawah nama penulis jurnal.	Sumbara,S.Kep.,Ners.,M.Kep
9.	Sabtu 22 Agustus 2020	1. Kurangi kata di abstrak, maksimal 250 kata, hilangkan yang bukan vokal. 2. Kata kunci semuanya berubah Bahasa inggris jika jurnalnya internasional semua. 3. Kata 'buah' dihapuskan menjadi 7 jurnal yang terindeks.. 4. ACC daftar sidang akhir.	Sumbara,S.Kep.,Ners.,M.Kep
10.	Sabtu 29 Agustus 2020	Sidang akhir	Sumbara,S.Kep.,Ners.,M.Kep
11.	Jum'at 11 September 2020	1. Evaluasi Post Sidang Akhir 2. ACC draft Skripsi	Sumbara,S.Kep.,Ners.,M.Kep

Daftar Periksa Penilai Kritis *JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)*

Peninjau :

Penulis :

Tanggal & Tahun :

catatan nomor :

	Ya	Tidak	Tidak jelas	Tidak berlaku
1. Dalam penelitian dapat dibedakan secara jelas antara "sebab" dan "akibat" (tidak ada kebingungan dalam menentukan variabel)?	☐	☐	☐	☐
2. Apakah partisipan memiliki kriteria inklusi yang sama?	☐	☐	☐	☐
3. Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	☐	☐	☐	☐
4. Apakah ada grup kontrol ?	☐	☐	☐	☐
5. Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	☐	☐	☐	☐
6. Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	☐	☐	☐	☐
7. Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?	☐	☐	☐	☐
8. Apakah penelitian diukur dengan cara yang tepat?	☐	☐	☐	☐
9. Apakah analisis statistic yang digunakan sesuai?	☐	☐	☐	☐

Penilaian keseluruhan:

☐ Sertakan

☐ kecualikan

☐ cari info lebih lanjut

Komentar (Termasuk alasan pengecualian)

Daftar Periksa Penilai Kritis *JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)*

Peninjau : Madaniawati

Penulis : Xiang Si, Di-Yin Chao, Juan Chen, Zi-Meng Liu, et al

Tanggal & Tahun : 15-8-2017

catatan nomor : 10.4103/0366-6999.223841

	Ya	Tidak	Tidak jelas	Tidak berlaku
1. Dalam penelitian dapat dibedakan secara jelas antara "sebab" dan "akibat" (tidak ada kebingungan dalam menentukan variabel)?	V	☐	☐	☐
2. Apakah partisipan memiliki kriteria inklusi yang sama?	V	☐	☐	☐
3. Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	V	☐	☐	☐
4. Apakah ada grup control	V	☐	☐	☐
5. Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	V	☐	☐	☐
6. Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	V	☐	☐	☐
7. Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?	V	☐	☐	☐
8. Apakah penelitian diukur dengan cara yang tepat?	V	☐	☐	☐
9. Apakah analisis statistic yang digunakan sesuai?	V	☐	☐	☐

Penilaian keseluruhan:

☑ Sertakan

☐ kecualikan

☐ cari info lebih lanjut

Komentar (Termasuk alasan pengecualian)

Daftar Periksa Penilai Kritis *JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)*

Peninjau : Madaniawati

Penulis : Sebastian Preau, MD; Fabienne Saulnier, MD; Florent Dewavrin, MD, et all.

Tanggal & Tahun : 2010

catatan nomor : 10.1097/CCM.0b013e3181c8fe7a

	Ya	Tidak	Tidak jelas	Tidak berlaku
1. Dalam penelitian dapat dibedakan secara jelas antara "sebab" dan "akibat" (tidak ada kebingungan dalam menentukan variabel)?	V			
2. Apakah partisipan memiliki kriteria inklusi yang sama?	V			
3. Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	V			
4. Apakah ada grup control		V		
5. Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	V			
6. Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	V			
7. Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?				V
8. Apakah penelitian diukur dengan cara yang tepat?	V			
9. Apakah analisis statistic yang digunakan sesuai?	V			

Penilaian keseluruhan:

☑ Sertakan

☐ kecualikan

☐ cari info lebih lanjut

Komentar (Termasuk alasan pengecualian)

Daftar Periksa Penilai Kritis *JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)*

Peninjau : Madaniawati

Penulis : Sahil Chopra, Jordan Thompson, Shahab Shahangia, Suman Thapamagar, Dafne Moretta, Chris Gashs, Avi Cohen, H. Bryant Nguyen

Tanggal & Tahun : 27 September 2019

catatan nomor : doi.org/10.1371/journal.pone.0222956

	Ya	Tidak	Tidak jelas	Tidak berlaku
1. Dalam penelitian dapat dibedakan secara jelas antara "sebab" dan "akibat" (tidak ada kebingungan dalam menentukan variabel)?	V	☐	☐	☐
2. Apakah partisipan memiliki kriteria inklusi yang sama?	V	☐	☐	☐
3. Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	V	☐	☐	☐
4. Apakah ada grup control	V	☐	☐	☐
5. Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	V	☐	☐	☐
6. Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	V	☐	☐	☐
7. Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?	V	☐	☐	☐
8. Apakah penelitian diukur dengan cara yang tepat?	V	☐	☐	☐
9. Apakah analisis statistic yang digunakan sesuai?	V	☐	☐	☐

Penilaian keseluruhan:

☑ Sertakan

☐ kecualikan

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Komentar (Termasuk alasan pengecualian)

Daftar Periksa Penilai Kritis *JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)*

Peninjau : Madaniawati

Penulis : Caibao Hu, Guolong Cai, Jing Yan, Hongjie Tong, Xiaochun Lv, et all

Tanggal & Tahun : 25 Mei 2017

catatan nomor : doi: 10.21037/jeccm.2017.04.02

	Ya	Tidak	Tidak jelas	Tidak berlaku
1. Dalam penelitian dapat dibedakan secara jelas antara "sebab" dan "akibat" (tidak ada kebingungan dalam menentukan variabel)?	V			
2. Apakah partisipan memiliki kriteria inklusi yang sama?	V			
3. Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	V			
4. Apakah ada grup control		V		
5. Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	V			
6. Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	V			
7. Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?				V
8. Apakah penelitian diukur dengan cara yang tepat?	V			
9. Apakah analisis statistic yang digunakan sesuai?	V			

Penilaian keseluruhan:

☑ Sertakan

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Komentar (Termasuk alasan pengecualian)

Daftar Periksa Penilai Kritis *JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)*

Peninjau : Madaniawati

Penulis : Zhou-zhou Dong, Qiang Fang, Heng Shi

Tanggal & Tahun : 2012

catatan nomor : 10.5847/ wjem.j.issn.1920–8642.2012.03.006

	Ya	Tidak	Tidak jelas	Tidak berlaku
1. Dalam penelitian dapat dibedakan secara jelas antara "sebab" dan "akibat" (tidak ada kebingungan dalam menentukan variabel)?	V			
2. Apakah partisipan memiliki kriteria inklusi yang sama?	V			
3. Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	V			
4. Apakah ada grup control		V		
5. Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	V			
6. Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	V			
7. Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?				V
8. Apakah penelitian diukur dengan cara yang tepat?	V			
9. Apakah analisis statistic yang digunakan sesuai?	V			

Penilaian keseluruhan:

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Komentar (Termasuk alasan pengecualian)

Daftar Periksa Penilai Kritis *JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)*

Peninjau : Madaniawati

Penulis : Julien Pottecher, Stephane Deruddre, Jean Luois Teboul, Jean-Frncois Georger, Christian Laplace, Dan Benhamou, Eric Vicaut, Jacques Duranteau

Tanggal & Tahun : 14 April 2010

catatan nomor : 10.1007/s00134-010-1973-

	Ya	Tidak	Tidak jelas	Tidak berlaku
1. Dalam penelitian dapat dibedakan secara jelas antara "sebab" dan "akibat" (tidak ada kebingungan dalam menentukan variabel)?	V			
2. Apakah partisipan memiliki kriteria inklusi yang sama?	V			
3. Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	V			
4. Apakah ada grup control		V		
5. Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	V			
6. Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	V			
7. Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?				V
8. Apakah penelitian diukur dengan cara yang tepat?	V			
9. Apakah analisis statistic yang digunakan sesuai?	V			

Penilaian keseluruhan:

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Daftar Periksa Penilai Kritis *JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)*

Peninjau : Madaniawati

Penulis : Nicolaj Duus, Daniel J. Shogilev, MD, Simon Skibsted, MD

Tanggal & Tahun : 2015

catatan nomor : dx.doi.org/10.1016/j.jnc.2014.07.031

	Ya	Tidak	Tidak jelas	Tidak berlaku
1. Dalam penelitian dapat dibedakan secara jelas antara "sebab" dan "akibat" (tidak ada kebingungan dalam menentukan variabel)?	V			
2. Apakah partisipan memiliki kriteria inklusi yang sama?	V			
3. Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	V			
4. Apakah ada grup control ?		V		
5. Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	V			
6. Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	V			
7. Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?				V
8. Apakah penelitian diukur dengan cara yang tepat?	V			
9. Apakah analisis statistic yang digunakan sesuai?	V			

Penilaian keseluruhan:

☑ Sertakan

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☐ cari info lebih lanjut

Komentar (Termasuk alasan pengecualian)

Nomor Jurnal		1	2	3	4	5	6	7
1.	Dalam penelitian dapat dibedakan secara jelas antara “sebab” dan “akibat” (tidak ada kebingungan dalam menentukan variabel)?	Ya	Ya	Ya	Ya	Ya	Ya	Ya
2.	Apakah partisipan memiliki kriteria inklusi yang sama?	Ya	Ya	Ya	Ya	Ya	Ya	Ya
3.	Apakah partisipan yang masuk dalam penelitian menerima perlakuan yang sama?	Ya	Ya	Ya	Ya	Ya	Ya	Ya
4.	Apakah ada grup kontrol ?	Ya	Tidak	Ya	Tidak	Ya	Tidak	Tidak
5.	Apakah ada pengukuran hasil sebelum dan sesudah intervensi?	Ya	Ya	Ya	Ya	Ya	Ya	Ya
6.	Apakah Tindakan dilakukan secara lengkap. Jika tidak apakah perbedaan kelompok tindak lanjutnya dijelaskan dan dianalisis secara memadai?	Ya	Ya	Ya	Ya	Ya	Ya	Ya
7.	Apakah hasil pengukuran partisipan yang masuk sebagai partisipan diukur dengan cara yang sama?	Ya	Tidak Berlaku	Ya	Tidak Berlaku	Tidak Berlaku	Tidak Berlaku	Tidak Berlaku
8.	Apakah penelitian diukur dengan cara yang tepat?	Ya	Ya	Ya	Ya	Ya	Ya	Ya
9.	Apakah analisis statistic yang digunakan sesuai?	Ya	Ya	Ya	Ya	Ya	Ya	Ya

Judul : *Effect of Systolic Cardiac Function on Passive Legs Raising for Predicting Fluid Responsiveness: a Prospective Observational Study* Subjek Penelitian : 78 klien syok sepsis yang terpasang ventilasi mekanik yang masuk kedalam kriteria inklusi. *Phenomena of interest :* kemampuan *passive legs raising* dalam menilai responsivitas cairan masih jarang untuk dilaporkan. Sehingga penelitian ini mencoba menggali lebih dalam terkait dengan *systolic cardiac filling* yang dihitung dari *global ejection fraction* (GEF) menggunakan *transpulmonary-thermodilution* untuk menilai secara diagnostic kemampuan PLR dalam menilai responsivitas cairan.					
Synthesized finding (temuan sintesis)	*Type of research* (jenis penelitian)	*Dependability* (keteguhan/hal yang dapat dipercaya)	*Credibility* (kepercayaan)	*Concual score* (skor konseptual)	Comments
Akurasi PLR dalam menilai responsivitas cairan bergantung pada *systolic cardiac function.* Delta SV dan *Cardiac Output* adalah parameter yang secara akurat dalm mengukur responsivitas cairan.	*Quasi Experimental Study*	4-5 '*yes' response : the finding remains unchanged*	*No change*	Tinggi *(High)*	*All unequivocal findings*

Judul : *Passive Legs Raising is predictive fluid responsiveness in spontaneously breathing patient with severe sepsis or acute pancreatitis.* Subjek Penelitian : 39 klien yang masuk kepada kriteria inklusi. *Phenomena of interest :* Pemberian terapi cairan secara cepat masih menjadi perdebatan, karena pemberian cairan tidak selalu meningkatkan hemodinamik status, sehingga dibutuhkan parameter untuk menilai responsivitas cairan. Context : Subjek dipilih secara acak dari 13 Rumah sakit di Inggris dan Amerika					
Synthesized finding (temuan sintesis)	*Type of research* (jenis penelitian)	*Dependability* (keteguhan/hal yang dapat dipercaya)	*Credibility* (kepercayaan)	*Concual score* (skor konseptual)	Comments
Passive Legs Raising dapat menyebabkan perubahan pada stroke volume dan merupakan parameter yang secara akurat dapat menilai responsivitas cairan pada klien sepsis yang terpasang ventilator. Perubahan pada *stroke volume, radial pulse pressure, dan peak velocity of femoral artery* yang disebabkan oleh PLR bisa memprediksi responsivitas cairan secara akurat pada klien yang tidak terintubasi.	*Quasi-Experimental Studies*	4-5 '*yes' response : the finding remains unchanged*	*No change*	Tinggi *(High)*	*All unequivocal findings*

Judul : *Precision and consistency of the passive leg raising manuver for determining fluid responsiveness with bioreactance noninvasive cardiac output monitoring in critically ill patients and healthy volunteers* Subjek Penelitian : Tujuh puluh lima orang klien de dan dua puluh lima *volunteers* *Phenomena of interest :*					
Synthesized finding (temuan sintesis)	*Type of research* (jenis penelitian)	*Dependability* (keteguhan/hal yang dapat dipercaya)	*Credibility* (Kepercayaan)	*Concual score* (skor konseptual)	Comments
Ketepatan dan konsistensi PLR dalam menilai responsivitas cairan pada klien sepsis menggunakan NICOM memiliki implikasi jika nilai SVV lebih besar dri 10% yang merupakan nilai *cut of* untuk menilai responsivitas cairan.	*Quasi Experimental Study*	4-5 '*yes' response : the finding remains unchanged*	*No change*	*Tinggi (high)*	*All unequivocal findings*

Judul : *Bioreactance based Passive Legs Raising test can predict fluid responsiveness in elderly pastient with septic shock.*
Subjek Penelitian : 50 klien syok sepsis yang sudah berusia lanjut di Departement of critical care Medicine of Zhejiang Hospital October 2012 to October 2015.
Phenomena of interest : Beberapa penelitian sebelumnya melaporkan tentang evaluasi PLR dalam menilai responsivitas cairan pada klien yang berusia lanjut namun tidak spesifik pada klien sepsis. Sehingga penelitian ini mencoba untuk memprediksi nilai bioreactance dalam menilai responcivitas cairan pada klien sepsis yang berusia lanjut, dibandingkan dengan nilai CVP.

Synthesized finding (temuan sintesis)	*Type of research* (jenis penelitian)	*Dependability* (keteguhan/hal yang dapat dipercaya)	*Credibility* (kepercayaan)	*Concual score* (skor konseptual)	Comments
PLR bisa menilai responsivitas cairan pada klien syok sepsis yang berusia lanjut, sedangkan CVP tidak bisa.	*Quasi Experimental Study*	4-5 '*yes' response : the finding remains unchanged*	*No change*	Tinggi *(high)*	*All unequivocal findings*

Judul : *Passive Legs Raising as an indictor of fluid responsiveness in patient with severe sepsis* Subjek Penelitian : 32 klien yang masuk kepada kriteria inklusi. *Phenomena of interest :* pengkajian responsivitas cairan pada klien kritis sebelum pemberian terapi klien masih menjadi dilemma. Indicator hemodinamik statis masih menjadi predictor yang lemah. Sehingga penelitian ini dilakukan untuk mengetahui efektifitas PLR dalam menilai responsivitas cairan pada klien sepsis yang terpasang ventilasi mekanik.					
Synthesized finding (temuan sintesis)	*Type of research* (jenis penelitian)	*Dependability* (keteguhan/hal yang dapat dipercaya)	*Credibility* (kepercayaan)	*Concual score* (skor konseptual)	Comments
Perubahan *Stroke Volume Index (SVI)* dan CVP yang disebabkan oleh PLR adalah indikator akurat dalam menilai responsivitas cairan pada klien sepsis yang dipasang ventilasi mekanik.	*Quasi-Experimental Studies*	4-5 '*yes' response : the finding remains unchanged*	*No change*	Tinggi (*High)*	*All unequivocal findings*

Judul : *Both Passive Legs Raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patient.*
Subjek Penelitian : 25 klien syok sepsis yang terpasang ventilasi mekanik
Phenomena of interest : Pemberian terapi cairan bisa meningkatkan aliran darah mikrosirkulasi melalui efek sistemik (peningkatan *cardiac output* dan tekanan perfusi di perifer. Untuk mengkaji kemampuan tubuh dalam pemberian terapi cairan perlu dilakukan pengkajian terhadap responsivitas cairan dengan membandingkan antara *passive legs raising* dan *volume expansion.*

Synthesized finding (temuan sintesis)	*Type of research* (jenis penelitian)	*Dependability* (keteguhan/hal yang dapat dipercaya)	*Credibility* (kepercayaan)	*Concual score* (skor konseptual)	Comments
PLR secara signifikan dapat meningkatkan CO dan secara signifikan menurunkan *pulse pressure* sehingga bisa dijadikan sebagai pengkajian awal dalam menilai responsivitas cairan. Pada klien syok sepsis yang datang ke RS dalam 24 jam pertama, baik PLR ataupun VE dapat mneingkatkan *sublingual microcirculatory perfusion*. PLR bisa digunakan sebagai cara yang efektif dalam menilai responsivitas cairan.	*Analytical Cross Sectional Studies*	4-5 '*yes' response : the finding remains unchanged*	*No change*	Tinggi *(High)*	*All unequivocal findings*

Judul : *The reliability and validity of passive legs raise and fluid bolus to assess fluid responsiveness in spontaneously breathing emergency department patients.* Subjek Penelitian : 109 orang klien sepsis yang datang ke Unit Gawat Darurat *Phenomena of interest :* masih terbatasnya penelitian tentang penilaian responsivitas cairan di ruangan IGD, terutama pada klien sepsis yang bernafas spontan.					
Synthesized finding (temuan sintesis)	*Type of research* (jenis penelitian)	*Dependability* (keteguhan/hal yang dapat dipercaya)	*Credibility* (kepercayaan)	*Concual score* (skor konseptual)	Comments
PLR dapat menilai responsivitas cairan pada klien sepsis menggunakan NICOM untuk klien di unit gawat darurat dan merekomendasikan PLR untuk dilakukan dalam menilai responsivitas cairan dibandingkan dengan *fluid bolus.*	*Quasi Experimental Study*	4-5 '*yes' response : the finding remains unchanged*	*No change*	Tinggi *(High)*	*All unequivocal findings*

Bulan	**Maret**				**April**				**Mei**				**Juni**				**Juli**				**Agustus**				**September**	
Minggu Ke-	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**
Kegiatan																										
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Mencari jurnal-jurnal ilmiah																										
Melakukan analisa data																										
Membuat pembahasan serta kesimpulan																										
Melakukan ujian sidang *literature review*																										
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Original Article

Bioreactance-based passive leg raising test can predict fluid responsiveness in elderly patients with septic shock

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Background: Few studies have reported the value of volume responsiveness evaluation on bioreactancebased passive leg raising (PLR) test in elderly patients.This study was carried out to determinate the predictive value of bioreactance-based PLR test for predicting fluid responsiveness (FR) of elderly patients with septic shock, and to compare it to central venous pressure (CVP).

Methods: This prospective, single-centre study enrolled 50 elderly patients with septic shock from the Department of Critical Care Medicine of Zhejiang Hospital, Hangzhou, China, from October 2012 to October 2015. All patients underwent PLR test and fluid infusion test sequentially. Noninvasive cardiac output monitoring (NICOM) was used to continuously record hemodynamic parameters such as cardiac output (CO), heart rate (HR) and CVP, at baseline 1, PLR, baseline 2, and volume expansion (VE). FR is defined as the change in CO (ΔCO) ≥10% after the fluid infusion test.

Results: CO clearly increased after PLR and VE (5.21±2.34 *vs*. 6.03±2.73, P<0.05; 5.09±1.99 *vs*. 5.60±2.11, P<0.05). The PLR induced change in CO (ΔCOPLR) and VE induced change in CO (ΔCOVE) were highly correlated [r=0.80 (0.64–0.90)], while the CVP and ΔCOVE were uncorrelated [r=0.12 (−0.16–0.32)]. The areas under the ROC curves of ΔCOPLR and CVP predicting FR were 0.868 and 0.514 respectively.

ΔCOPLR ≥10% was found to predict FR with a sensitivity of 86% and a specificity of 79%.

Conclusions: Bioreactance-based PLR tests could predict FR of elderly patients with septic shock, while CVP could not.

Keywords: Passive leg raising (PLR); septic; volume responsiveness; septic shock; volume; expansion

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Introduction

Fluid management is of critical importance and challenging during the treatment of patients with septic shock. Positive fluid therapy could effectively improve the hemodynamic stability, decrease the complication and mortality of patients (1). However, this approach is not always benefit to patients, it is associated with many risks, such as acute heart failure and acute pulmonary edema especially for elderly patients. Thus, accurately predicting fluid responsiveness (FR) and thus to estimate whether the patient will benefit from fluid therapy seems particularly important. Recent studies have demonstrated that one simple effective method for predicting FR is passive leg raising (PLR) test (2).

Researchers could estimate whether the patient is fluid responsive through monitoring the hemodynamic changes before and after PLR. This study intends to predict FR of elderly patients with septic shock using bioreactance-based noninvasive cardiac output monitoring (NICOM) PLR test, to evaluate the value of this approach and compare to the central venous pressure (CVP) for predicting FR.

Methods

1.3.Patients

Patients over 60 years old with septic shock were enrolled from the Department of Critical Care Medicine of Zhejiang Hospital, Hangzhou, China, from October 2012 to October 2015. Diagnostic criteria for sepsis were as per the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM), on the basis of infection occurring accompanied by at least two of the following: (I) body temperature › 38.3 or <36 ℃; (II) heart rate (HR) › 90 beats/min; (III) respiratory › 20 beats/min or $PaCO_2$ <32 mmHg; (IV) white blood cell (WBC) count › 12×10^9/L or <4×10^9/L or normal WBC count with greater than 10% immature forms. Septic shock was defined as sepsis-induced hypotension. The inclusion criteria were one or more of the following signs of tissue hypoperfusion: (I) systolic blood pressure <90 mmHg or decreased more than 40 mmHg compared to baseline level; (II) hourly urine output <0.5 mL/kg for more than 2 h; (III) HR › 100 beats/min; (IV) skin mottling. The exclusion criteria were as follows: (I) less than 60 years; (II) intra-abdominal hypertension (intraabdominal pressure › 16 mmHg) (3); (III) organic heart disease (such as: mitral valve stenosis or intracardial shunt); (IV) intracranial hemorrhage or potential intracranial hemorrhage; (V) NICOM signal instability; (VI) other types of shock. This study was approved by the Ethics Committee of Zhejiang Hospital.

1.4.Measurements

Two dual-electrode stickers were placed on the right side of the chest wall, while another two stickers were placed on the left and connected to the NICOM system (Cheetah Medical, USA) for continuous recording of the following hemodynamic parameters: CO, HR, and noninvasive blood pressure (NIBP). Subclavian or jugular vein catheters (Arrow, USA) were put in place and connected to the monitor (Philips Healthcare, MP20, Germany) to record CVP.

1.5.Protocol

Patients enrolled in this study were managed with the following protocol. Baseline 1: patients were placed in a semi-recumbent position with the head of the bed elevated to 45° and the foot of the bed remaining horizontal; PLR: patients were placed in a supine position with their lower limbs elevated to 45°; baseline 2: patients were in a semirecumbent position

again, the same as in baseline 1; volume expansion (VE): 250 mL of normal saline solution was infused

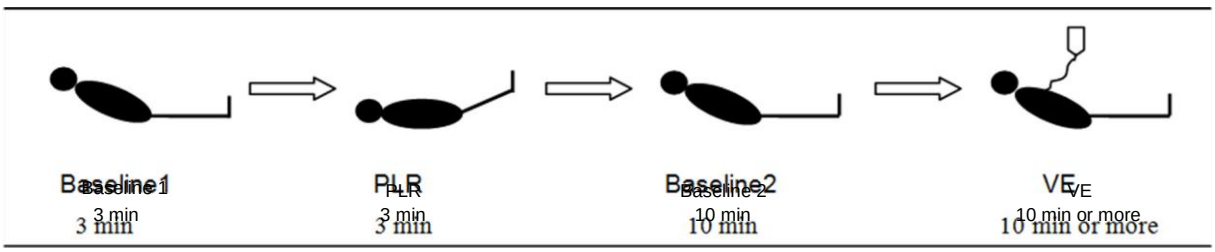


Figure 1 Diagram of the study protocol. PLR, passive leg raising; VE, volume expansion.

through the vein catheters within approximately 10 min. The NICOM system was used to record hemodynamics minute by minute during the 26 min or more, including: (I) 3 min of baseline 1; (II) 3 min of PLR; (III) 10 min of baseline 2; (IV) 10 min or more of VE (*Figure 1*). Throughout the protocol the ventilator parameters and the dosage of the vasoactive agents remained unchanged. Patients whose cardiac output (CO) increased by ≥10% were defined as responders, while those whose CO increased by <10% were defined as non-responders. This study was approved by the Ethics Committee of Zhejiang Hospital, with all the patients and their families have signed informed consent forms before participating in the study.

1.6.Statistics

Data were expressed as mean and standard deviation (SD). PLR induced change in CO was calculated as follows: ΔCOPLR% = [(CO after PLR) − (CO before PLR)] ×100/ (CO before PLR). VE induced change in CO was calculated as follows: ΔCOVE% = [(CO after VE) − (CO before VE)] ×100/(CO before VE). Comparisons of hemodynamic variables before and after intervention were made using paired *t*-test, and the comparisons between responders and non-responders were conducted using a two-sample *t*-test. The Pearson correlation coefficient was used to measure the linear correlations between ΔCOPLR% and ΔCOVE%, and between CVP and ΔCOVE%. All statistical tests were performed using SPSS (version 21.0, IBM, NY, USA), with $P<0.05$ being considered statistically significant.

Results

Demographic data of the 50 patients tested is presented in *Table 1*. Nearly half of the patients were treated with vasoactive agents. There were no significant differences

Table 1 Patient demographics

Characteristics	Outcome
Age (years)	81±9
Gender (M/F)	26/24
Height (cm)	167±7
Weight (kg)	66±11
BSA (m^2)	1.71±0.17
Sources of infection (n)	
Pulmonary	35
Abdominal	9
Urological	5
Others	1
Dosage of vasoactive agents (μg/kg/min)	
Norepinephrine	0.34±0.18
Dopamine	7.51±3.23
Dobutamine	8.48±2.09

BSA, body surface area.

in heights, weights, ages, body surface areas (BSA), and dosages of norepinephrine and dopamine between the two groups (P › 0.05).

1.7. Effects of PLR and VE on hemodynamics

Among the 50 patients, 26 were responders and 24 were non-responders. In responders, compare to their baseline CO increased obviously after PLR and VE (P<0.05), while in non- responders compare to their baseline CO didn't increase obviously (P › 0.05). In responders and non- responders, the changes in HR before and after PLR and VE were not statistically significant (P› 0.05) (*Table 2*).

1.8. Analysis of correlation coefficient values

There was a good correlation between PLR induced change in CO (ΔCOPLR) and VE induced change in CO (ΔCOVE) [r=0.80 (0.64–0.90)] (*Figure 2*), and there was no correlation between VE induced change in CO (ΔCOVE) and CVP

[r=0.12 (−0.16–0.32)].

1.9.Values of ΔCOVE and CVP for predicting FR

The area under the ROC curve of CVP and PLR induced changes in CO (ΔCOPLR) for predicting FR was 0.477 and 0.883 respectively. The ΔCOPLR ≥10% was found to predict FR with a sensitivity of 86% and specificity of 79% (*Figure 3*).

Discussion

Our study showed that bioreactance-based PLR test is a simple and accurate method to predict FR in elderly patients with septic shock and CVP is hardly have the demanded accuracy for predicting FR. The percentage of CO response to PLR correlated very closely to the change of CO induced by fluid infusion test while the CVP didn't. Our finding is in accordance with Benomar's study that it is valid to use the bioreactance-based NICOM system to predict FR from changes in CO during PLR with patients after cardiac surgery (4). And Marik's study enrolled 34 hemodynamic unstable ICU patients (5), indicating that bioreactancebased PLR test is accuracy enough for predicting FR in a large amount of patients.

Fluid therapy is a usual approach in the management of hemodynamic unstable ICU patients, whether for patients with septic shock or any other patients, positive fluid therapy could increase CO and thus to improve the tissue perfusion prognosis and to decrease the mortality of

Table 2 Effects of passive leg raising maneuver and volume expansion on hemodynamics

Parameters	Responders				Non-responders			
	Baseline 1	PLR	Baseline 2	VE	Baseline 1	PLR	Baseline 2	VE
CO (L/min)	5.21±2.34	6.03±2.73[a]	5.09±1.99	5.60±2.11[b]	5.24±1.25	5.40±1.40	5.18±1.04	5.21±1.24
HR (beats/min)	90±20	91±20	90±22	89±21	90±21	90±22	90±21	91±20
SBP (mmHg)	107±20	118±21[a]	117±18	124±19[b]	117±27	118±25	119±23	120±22
DBP (mmHg)	65±12	70±10[a]	67±11	69±10[b]	64±12	66±13	64±11	64±12
MAP (mmHg)	81±12	86±14[a]	81±13	87±12[b]	81±15	82±15	82±13	83±14
CVP (mmHg)			6±4	7±4			7±4	9±5

[a], P<0.05 versus baseline 1; [b], P<0.05 versus baseline 2. CO, cardiac output; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CVP, central venous pressure; PLR, passive leg raising; VE, volume expansion.

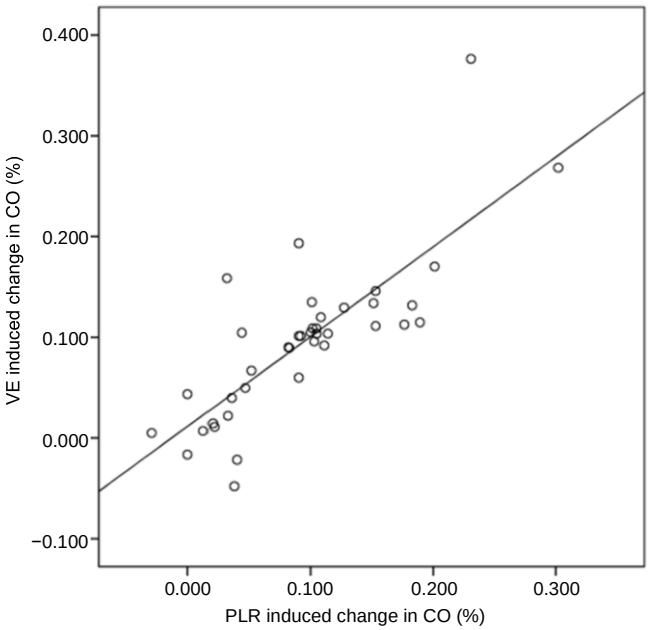


Figure 2 Relationship between PLR induced change in CO (%) and VE induced change in CO (%). CO, cardiac output.

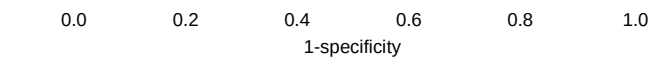
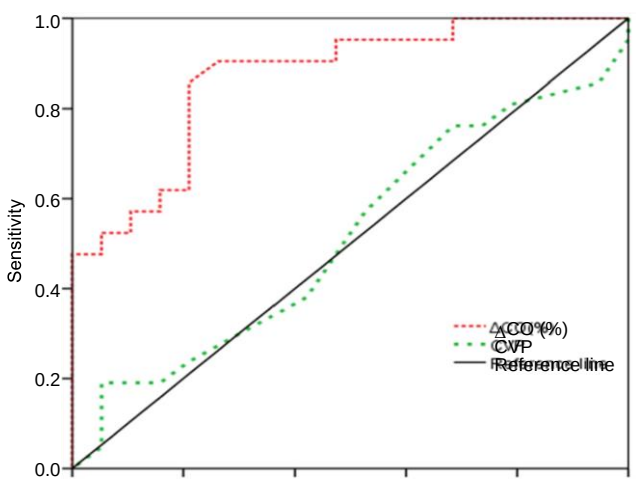


Figure 3 Comparison of receiver operating characteristic curves regarding the ability to discriminate responders and nonresponders. ΔCO (%): passive leg raising induced changes in cardiac output. CVP, central venous pressure.

patients. However, inappropriate fluid therapy will cause many complications and thus bring about undesirable outcomes. Consequently, during the past decades countless efforts have been made to accurately predicting FR, from the static indicators to predictors based on heartlung interactions such as SVV and PPV, but all have some limitations (6,7).

Recent researches have shown that a simple safe method is PLR test. By elevating the lower limbs to 45°, inducing passive transfer of blood contained in the venous compartment of the lower limbs and of the abdominal compartments to the heart, it thus can increase about 300 mL cardiac preload of the heart (2,8). A large number of studies (9-11) have designed to test its reliability for predicting FR and a meta-analysis (12) have confirmed its diagnostic accuracy. PLR serve as a “self-volume challenge”, it is simple, reliable and safe, since the influence of PLR to cardiac preload will disappear immediately when the



elevated limbs are horizontal again (8).

Although PLR is an effective way for predicting FR, it must perform under the guidance of technologies such as pulse index continuous CO (PICCO) (11) and echocardiography (9). Therefore, predicting FR based on CVP is widely used in critical care setting for its convenience and low costs. However, our study showed that there was a very low correlation between the change of CO after giving fluid bolus and CVP at baseline 2 suggesting that CVP is not useful in predicting FR. It is also confirmed by a meta-analysis in recent years which included ten studies that the correlation coefficient between CVP and change in stroke index/cardiac index was poor (r=0.18) (13). CVP represents the pressure of right atrium and near superior and inferior vena cava, can not reflect the true blood volume. Moreover, the measurement of CVP is greatly influenced by artificial factors such as the proficiency of operator and the position of the sensor. Maybe it can partly explain the reason why CVP performs so badly in predicting FR.

For the past years, physicians devoted to develop more efficient devices for hemodynamic monitoring. There is no doubt that the most ideal device should be accurate noninvasive easy to use and cheap. NICOM is such a new device for noninvasive hemodynamic measuring. It is based on an analysis of relative phase shifts of an oscillating current that occur when this current traverses the thoracic cavity to calculate the hemodynamic parameters and just need four double-electrode stickers placed on the chest wall (14). Comparing with the thermodilution which serves as the "gold standard" of hemodynamic measurements, its accuracy has already been demonstrated in the previous studies (15,16). In addition, it has a shorter response time for hemodynamic challenges (17) which is emphasized in the daily work. Clinical determination of giving a fluid bolus is depend on whether the patient will benefit from it, thus a method that is accuracy, easy to get, efficient is preferable, for predicting FR. Considering this there is no doubt that bioreactancebased PLR test can be routinely used to predict FR, since the assessment could be finished in 6 min.

In a recent study, Kupersztych-Hagege and his colleagues found that the correlation between the changes in pulse contour analysis-derived CI and NICOM derived CI induced by VE is very poor (18), demonstrating that bioreactance-based PLR test may fail to predict FR. The reasons may be as follows, first, the degree of bioimpedance unreliability was related to the extent of lung injury and fluid accumulation within the thorax (19), and maybe so is the bioreactance VE would reduce haemoglobin levels and possibly alter the bioreactance readings. In this study, although all the participants were patients with septic shock, there was no occurrence of acute respiratory distress syndrome and pulmonary edema in these 80 patients, what's more we only used half of the fluid, maybe it is the main difference between the two studies. Although we found a relatively

ideal result, we believe that any new device will confront many problems during the progress of clinical popularization. These were the very aspects that the following study should focus more on.

In this study, we used 250 mL normal saline, instead of the commonly used 500 mL (9-11), to perform a volume challenge. Firstly, because clinical use of fluid to perform a fluid infusion test is 250 mL normal saline; secondly, only about 50% of critically ill patients were fluid responders (8), the patients enrolled in this study were mostly the elders, these patients have a decreased number of myocardial cells and hyperplasia of collagen tissues, thus having a higher risk of heart failure, using this volume of fluid is to reduce the detrimental effects.

Our study had some limitations. First, all the patients were septic shock. Therefore, it is not known whether or not our results can be extrapolated to other populations for whom fluid optimization is necessary for treatment. Second, we excluded patients with organic heart disease for fearing that it will in some extent influence the prediction of FR referring to Renner's study (20) without test it.

In conclusion, in the specific population of elderly patients we studied here, bioreactance-based PLR test but not CVP could accurately predict FR of elderly patients with septic shock. Because of its practicability and effectiveness, this approach deserves a further promotion in daily practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Ethics

Committee of Zhejiang Hospital (approval number: 201328). All the patients and their families have signed informed consent forms before participating in the study.

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RESEARCH ARTICLE

Precision and consistency of the passive leg raising maneuver for determining fluid responsiveness with bioreactance noninvasive cardiac output monitoring in critically ill patients and healthy volunteers

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Abstract

Objective

The passive leg raising (PLR) maneuver has become standard practice in fluid resuscitation. We aim to investigate the precision and consistency of the PLR for determining fluid responsiveness in critically ill patients and healthy volunteers using bioreactance non-invasive cardiac output monitoring (NiCOM™, Cheetah Medical, Inc., Newton Center, Massachusetts, USA).

Methods

This study is prospective, single-center, observational cohort with repeated measures in critically ill patients admitted to the medical intensive care unit and healthy volunteers at a tertiary academic medical center. Three cycles of PLR were performed, each at 20–30 minutes apart. *Fluid responsiveness* was defined as a change in stroke volume index (ΔSVI) > 10% with each PLR as determined by NiCOM™. *Precision* was the variability in ΔSVI after the 3 PLR's, and determined by *range*, *average deviation* and *standard deviation*. *Consistency* was the same fluid responsiveness determination of "Yes" (ΔSVI > 10%) or "No" (ΔSVI 10%) for all 3 PLR's.

Results

Seventy-five patients and 25 volunteers were enrolled. In patients, the precision was range of 17.2±13.3%, average deviation 6.5±4.0% and standard deviation 9.0±5.2%; and for volunteers, 17.4±10.3%, 6.6±3.8% and 9.0±6.7%, respectively. There was no statistical difference in the precision measurements between patients and volunteers. Forty-nine (65.3%) patients vs. twenty-four (96.0%) volunteers had consistent results, $p < 0.01$. Among those

with consistent results, twenty-four (49.0%) patients and 24 (100%) volunteers were fluid responsive.

Conclusions

The precision and consistency of determining ΔSVI with NiCOM™ after PLR may have clinical implication if ΔSVI > 10% is the absolute cutoff to determine fluid responsiveness.

Introduction

Fluid management decisions are a difficult but integral part of daily patient care. With the growing consensus that extremes of fluid balance may be detrimental, an accurate assessment of a patient's volume status is paramount [1–4]. Screening patients who are fluid responsive can appropriately identify those who would likely benefit from fluid resuscitation.

Fluid responsiveness as an increase in cardiac output (CO) in response to augmentation of preload is fundamentally based on the classical Frank-Starling curve [5, 6]. If preload augmentation does not increase CO, further intravenous fluids serve no purpose and may potentially be harmful. However, clinicians often face the challenge of accurately recognizing when a patient has reached this plateau on the Frank-Starling curve. One maneuver, which has gained acceptance in standard practice to predict fluid responsiveness, without possibly inappropriate fluid administration, is passive leg raising (PLR) [7–9].

With less invasive technologies becoming increasingly available, the gold standard of pulmonary artery (PA) catheterization to measure CO has naturally fallen out of favor. As such, the bioreactance-based Non-invasive Cardiac Output Monitor (NiCOM™, Cheetah Medical, Inc., Newton Center, Massachusetts, USA) became popular in recent years given its completely non-invasive platform using four skin sensor pads placed on the patient's thorax. It measures stroke volume (SV) by using time delays or phase shifts induced by thoracic blood flow during the transmission of electrical current between the sensors [10–12].

At our institution, the NiCOM™ technology has become a primary tool to guide fluid management. We utilize its built-in algorithm for determining fluid responsiveness with the PLR. We a priori accept the NiCOM™ to provide accurate measurements of SV and CO. However, we frequently observed variability in the measured change in stroke volume index (ΔSVI) based on PLR. While the *accuracy* of the PLR for predicting fluid responsiveness has been determined, we were unable to find published data on the *precision* and *consistency* of predicting fluid responsiveness in critically ill patients by PLR [13]. The purpose of this study was to determine the precision and consistency of the PLR in predicting fluid responsiveness utilizing the NiCOM™ technology in critically ill patients and healthy volunteers.

Materials and methods

Study design

This study is a single-center, prospective observational cohort, with repeated measures in critically ill patients admitted to the medical intensive care unit and healthy volunteers. The study was conducted at an academic tertiary-care medical center from June 2017 to January 2018.

Written informed consent was obtained from study participants or their legal representatives. The protocol was approved by the Loma Linda University Institutional Review Board.

Study participants

For the patient cohort, inclusion criteria were: 1) age 18 years, and 2) suspicion for hypovolemia or indicated for volume expansion due to any one of the following: hypotension (systolic blood pressure < 90 mm Hg or mean arterial pressure < 65 mm Hg), tachycardia (heart rate > 90 beats per min), blood lactate > 2.0 mmol/L, skin mottling, oliguria (urine output < 30 ml/hr), or requiring vasopressor/inotrope support. Patients were excluded if there was an active arrhythmia, bleeding causing hemodynamic instability, intra-abdominal hypertension, pelvic and/or lower extremity trauma/amputation preventing passive leg raising, pulmonary hypertension requiring chronic pulmonary vasodilator therapy, severe valvular heart disease, severe anatomic abnormalities of thoracic aorta, external pacemaker, or renal replacement therapy during the data collection period.

Healthy volunteers were enrolled if they were 18 years of age with self-reported unremarkable medical history, but then excluded if unable to tolerate PLR.

Study procedure and data collection

To ensure minimal variability, the PLR and data collection were performed only by the authors after they were provided with an in-depth training on the NiCOM™ technology by the manufacturer. Each PLR and associated hemodynamic parameters were performed and recorded as follows. The subject's head was raised to a semi-recumbent 45˚ position for 3 minutes with the legs flat in the bed. After a stable hemodynamic signal was achieved on the NiCOM™ system, baseline hemodynamic data was collected. The subject's head was then placed flat and the legs elevated to 30–45˚ for 3 minutes with a standardized wedge pillow. The second set of hemodynamic data was collected at the time of PLR "auto-transfusion". At the end of 3 minutes, changes (Δ) in stroke volume index (SVI) and cardiac index (CI) were displayed on the NiCOM™ monitor, stating whether or not the subject was fluid responsive. The subject was then placed back in pre-PLR position. The above procedure of obtaining baseline hemodynamic values, performing the PLR, and recording ΔSVI and ΔCI was considered one PLR cycle. We performed three PLR cycles, designated as PLR 1, PLR 2, and PLR 3, each separated by a rest period of 20 to 30 minutes (Fig 1).

In the patient cohort, if the subject was found to be fluid responsive during the PLR but hemodynamically stable, data collection was continued. Upon completion of the study procedure, the primary team caring for the patient was notified of the results. If the patient was found to be fluid responsive and unstable, or the patient became

hemodynamically unstable for any reason during data collection, the study procedure was aborted and the primary team was notified immediately. The study procedure was also aborted if during the data collection the patient required any new hemodynamic intervention, including titration of fluids, vasopressor and/or inotrope; or if the patient did not tolerate the PLR. Data collected from patients with the study procedure aborted were excluded from data analysis.

Subject demographic characteristics, hemodynamic parameters, Sepsis-related (or Sequential) Organ Failure Assessment (SOFA) score, laboratory values, admission diagnosis category, and the presence of vasopressor/inotrope and mechanical ventilation were recorded [14].

Measurements of fluid responsiveness, precision and consistency

The ΔSVI after the PLR was calculated by the NiCOM™ proprietary algorithm using the peak value of SVI during the PLR challenge phase divided by the average SVI during the baseline phase. *Fluid responsiveness* was defined as ΔSVI > 10% after PLR. *Precision* was the variability in ΔSVI in response to PLR. We calculated the precision of ΔSVI over the 3 cycles of PLR's by three methods: 1) range, 2) average deviation, and 3) standard deviation.

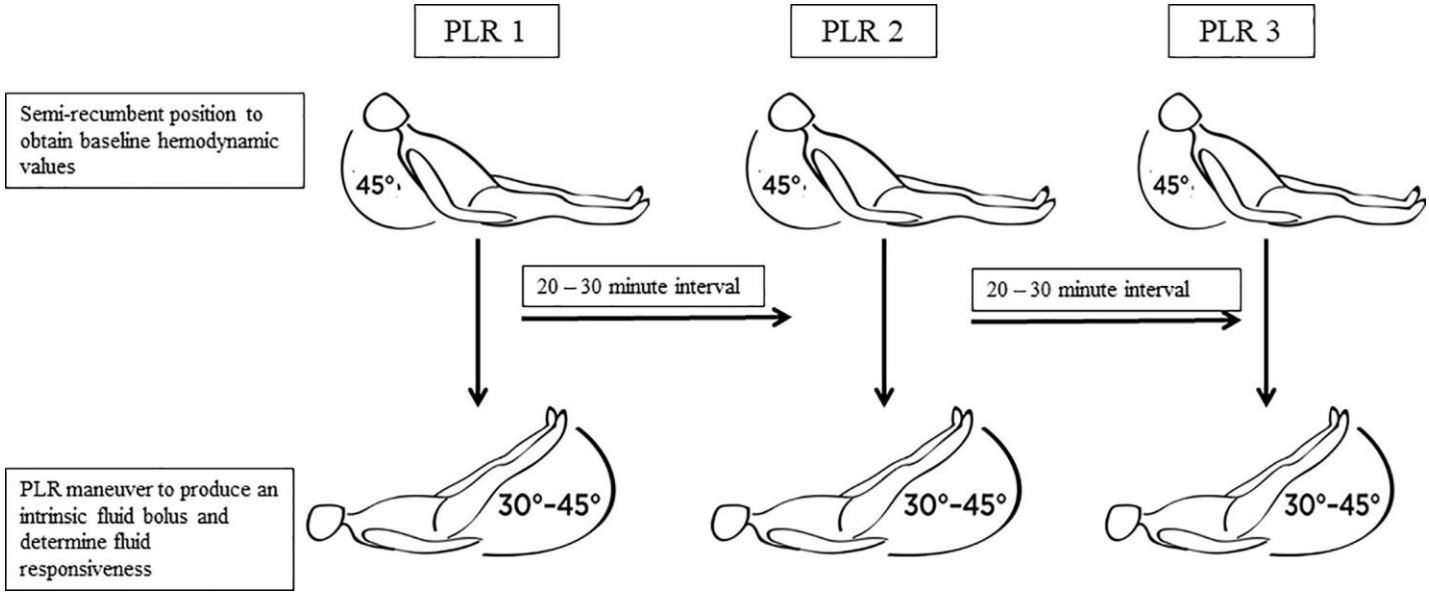

Fig 1. Serial passive leg raising (PLR) maneuver protocol. Patients were placed in the semi-recumbent position at 45˚ for 3 minutes and baseline hemodynamic values were recorded. PLR was induced by raising both lower extremities to 30–45˚ using a standard wedge pillow and held in this position for 3 minutes. After data collection, the patient was returned to the semi-recumbent resting position for 20–30 minutes. The PLR maneuver was repeated for 2 additional cycles.

Measurements of precision

Range = $x_{max} - x_{min}$ P$_{n¼PLR1}$ jx$_i$ ij

x

Average Deviation = $_i$

rffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiffiP$_{nPLRn^i¼PLR1}$ ðx$_i$ x$_i$Þ2

Standard Deviation = n_{PLR} 1

x_{max} = maximum ΔSVI from 3 cycles of PLR in the same subject x_{min} = minimum ΔSVI from 3 cycles of PLR in the same subject x_i = ΔSVI per PLR x_i = the mean of ΔSVI computed from 3 cycles of PLR in the same subject n_{PLR} = 3 (number of cycles of PLR in the same subject)

Consistency was defined as the same fluid responsiveness determination of "Yes"

(ΔSVI > 10%) or "No" (ΔSVI 10%) for all 3 cycles of PLR's. For example, a subject was categorized to have *consistent* results if they were persistently fluid responsive or not fluid responsive for all 3 PLR's. A subject had *inconsistent* results if any one of the 3 PLR's resulted in a fluid responsiveness determination that was different from the other PLR's.

Statistical analysis

Independent sample t-test, Mann Whitney or proportion chi-square was used to test for subject differences. Repeated measures analysis of variance was used to compare hemodynamic data over the 3 cycles of PLR's. Cohen's κ was calculated for agreement in determining fluid responsiveness of "Yes" (ΔSVI > 10%) or "No" (ΔSVI 10%) between two PLR's (PLR 1 vs. PLR 2, PLR 1 vs. PLR 3, and PLR 2 vs. PLR 3). Pearson's correlation coefficient (r) was calculated to determine the linear relationship between two PLR measurements of ΔSVI. Data are reported as mean±standard deviation. Categorical data are expressed as proportions. Data were analyzed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

1.10. Results

A total of 80 patients and 25 healthy volunteers were consented to participate in the study. Five patients were excluded: four due to a change of >1 mcg/min in norepinephrine dosage during the study procedure; and 1 withdrew their consent during the data collection period.

Final data analysis was performed on 75 patients and 25 healthy volunteers, with age 55.7± 19.8 vs. 32.8±11.8 years, respectively, $p < 0.01$ (Table 1). Patients had statistically significant higher body mass index, heart rate, lower mean arterial pressure, higher respiratory rate, and lower SVI than volunteers (all p 0.01). SOFA score was 7.0±4.8, lactate 3.1±3.9 mmol/L, 56% were on mechanical ventilation and 32% were receiving vasopressor/inotropic support.

There was no statistical difference in ΔSVI or ΔCI over the 3 cycles of PLR's in both patients and volunteers (Table 2). For patients, the linear relationship between ΔSVI's in each pair of PLR's (PLR 1 vs. PLR 2, PLR 1 vs. PLR 3, and PLR 2 vs. PLR 3) showed Pearson's correlation r = 0.66, 0.61 and 0.60, respectively (Fig 2A). For volunteers, r = 0.50, 0.58 and 0.75, respectively (Fig 2B). The agreement in determining fluid responsiveness between two PLR's in patients showed K = 0.55, 0.52 and 0.55, respectively.

The precision of ΔSVI over 3 cycles of PLR's was determined by *range*, *average deviation* and *standard deviation* (Table 3). Range was 17.2±13.3% and 17.4±10.3%, average deviation was 6.5±4.0% and 6.6±3.8%, and standard deviation was 9.0±5.2% and 9.0±6.7%, in patients and volunteers, respectively. There was no statistical difference in the precision measurements between patients and volunteers.

Forty-nine (65.3%) patients had consistent determination of fluid responsiveness for all 3 PLR's (Table 3). Among these, twenty-four (49.0%) patients were consistently fluid responsive and 25 (51.0%) were consistently *not* fluid responsive. Among volunteers, twenty-four (96.0%) had consistent determination of fluid responsiveness, with all those being fluid responsive (ΔSVI > 10%).

1.11. Discussion

We showed that the percent change in SVI measured by the NiCOM™ after a PLR has a precision of approximately ±9% (standard deviation) in both critically ill patients and healthy volunteers. While the *accuracy* of the PLR in predicting fluid responsiveness has been studied, our data suggest that the *precision* can change clinical decisions regarding fluid management when using this technology [13]. For example, a ΔSVI of 15% after PLR may be interpreted as 15±9%. In this scenario, should fluids be administered or should the PLR be repeated? If we repeat the PLR, our data showed that after 3 PLR's, ΔSVI would be consistent in 65% of patients and 96% of healthy volunteers using the cutoff of 10%.

Previous studies have shown that CO has a variation of 4.4 to 10.1% [15, 16]. However, repeated measures analysis of variance showed no significant differences between CO measurements [15]. Similarly, in our study, repeated measures analysis of variance showed no significant differences in ΔSVI amongst the 3 cycles of PLR's. Yet the variability (standard deviation) of 9% in ΔSVI has significant clinical ramification when a cutoff of 10% is used to determine fluid responsiveness by the NiCOM™.

In addition to spontaneous variation in CO measurements as explanation for our results, we used a bioreactance-based technology. While a number of studies have shown bioreactance to be a viable technology in determining fluid responsiveness coupled with the PLR, Kupersztych-Hagege et al. showed it to be unreliable when compared to thermodilution in measuring CI, with an error up to 82% and an area under the receiver operating characteristics curve not different from 0.5 for the ability of PLR induced ΔSVI to predict fluid responsiveness [17]. In a validation study by Squara et al., continuous CO measured by the NiCOM™ technology was

1. Patient and volunteer baseline characteristics. BMI–body mass index; SOFA–sequential organ failure assessment. Data are presented as mean ± standard deviation or as count (percentage).

Characteristic		Patients N = 75	Volunteers N = 25	*p-value*
Age (years)		55.7 ± 19.8	32.8 ± 11.8	<0.01
Sex				
	Male	36 (48.0)	16 (64.0)	0.17
	Female	39 (52.0)	9 (36.0)	0.17
Race				
	White	43 (57.3)	16 (64.0)	0.54
	Black	13 (17.3)	2 (8.0)	0.27
	Asian	5 (6.7)	7 (28.0)	<0.01
	Other	14 (18.7)	0 (0.0)	
BMI (kg/m^2)		27.1 ± 6.2	22.4 ± 3.0	<0.01
Hemodynamic characteristics				
	Heart rate (beats per min)	103.0 ± 18.8	66.0 ± 11.4	<0.01
	Mean arterial pressure (mm Hg)	76.0 ± 15.4	84.0 ± 13.3	0.01
	Respiratory rate (breaths per min)	21.0 ± 6.1	15.0 ± 3.0	<0.01
	Stroke volume index (mL/min/m^2)	33.5 ± 9.2	55.7 ± 10.3	<0.01
	Cardiac index (L/min/m^2)	3.3 ± 0.9	3.5 ± 0.6	0.08
	Total peripheral resistance (dynesec/cm^{-5})	1106.0 ± 499.9	1080.4 ± 398.5	0.79
Laboratories				
	Creatinine (mg/dL)	1.2 ±1.2	-	-
	Lactate (mMol/L)	3.1 ± 3.9	-	-
SOFA		7.0 ± 4.8	-	-
Hospital day (days)		5.0 ± 5.6	-	-
Admission diagnosis category				
	Sepsis	44 (58.7)	-	-

	Cardiac	11 (14.7)	-	-
	Respiratory	12 (16.0)	-	-
	Malignancy	2 (2.7)	-	-
	Metabolic	3 (4.0)	-	-
	Hematologic	3 (4.0)	-	-
	Renal	1 (1.3)	-	-
	Neurology	1 (1.3)	-	-
Presumed etiology of shock				
	Septic / distributive	41 (54.7)	-	-
	Cardiogenic	16 (21.3)	-	-
	Hypovolemic	3 (4.0)	-	-
	Obstructive	0 (0.0)	-	-
	Unknown	15 (20.0)	-	-
Reason for enrollment				
	Hypotension	26 (34.6)	-	-
	Tachycardia	59 (78.7)	-	-
	Skin mottling	3 (4.0)	-	-
	Lactate > 2.0mm/L	32 (42.7)	-	-
	Oliguria	12 (16.0)	-	-
	Vasopressor / inotropic support	24 (32.0)	-	-
Mechanical ventilation		42 (56.0)	-	-

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2. **Change in hemodynamic measurement with three cycles of passive leg raise (PLR) maneuvers.** SVI–stroke volume index; CI–cardiac index; ΔSVI–change in stroke volume index after the PLR maneuver; ΔCI–change in cardiac index after the PLR maneuver. Data are represented as mean ± standard deviation.

Patients N = 75	**PLR 1**		**PLR 2**		**PLR 3**		***p-value***
	Baseline	**After PLR**	**Baseline**	**After PLR**	**Baseline**	**After PLR**	

SVI (mL/min/m²)	33.0 ± 9.8	38 ± 11.5	33.4 ± 8.4	37.6 ± 11.2	34.2 ± 10.8	37.8 ± 12.1	-
CI (mL/min/m²)	3.3 ± 0.9	3.7 ± 1.0	3.3 ± 0.8	3.8 ± 1.0	3.4 ± 1.0	3.7 ± 1.0	-
ΔSVI (%)	-	14.5 ± 19.7	-	14.7 ± 18.5	-	13.2 ± 16.9	0.59
ΔCI (%)	-	14.7 ± 19.4	-	14.6 ± 19.2	-	12.7 ± 17.4	0.59
Volunteers N = 25							
SVI (mL/min/m²)	55.7 ± 10.4	74.4 ± 13.2	53.0 ± 9.7	71.9 ± 13.7	51.6 ± 10.6	71.2 ± 14.6	-
CI (mL/min/m²)	3.5 ± 0.6	4.6 ± 0.8	3.3 ± 0.5	4.3 ± 0.8	3.1 ± 0.6	4.26 ± 0.9	-
ΔSVI (%)	-	34.7 ± 14.3	-	36.1 ± 13.8	-	39.2 ± 19.9	0.68
ΔCI (%)	-	30.6 ± 12.5	-	32.2 ± 13.7	-	35.8 ± 17.3	0.69

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compared to the PA catheter. During periods of stable CO, the precision (defined as 2 standard deviation / mean) of CO measured by NiCOM™ was 12±7% [12]. Stetz et al. had previously shown that a difference of 12–15% in CO measurements may suggest clinical significance [18].

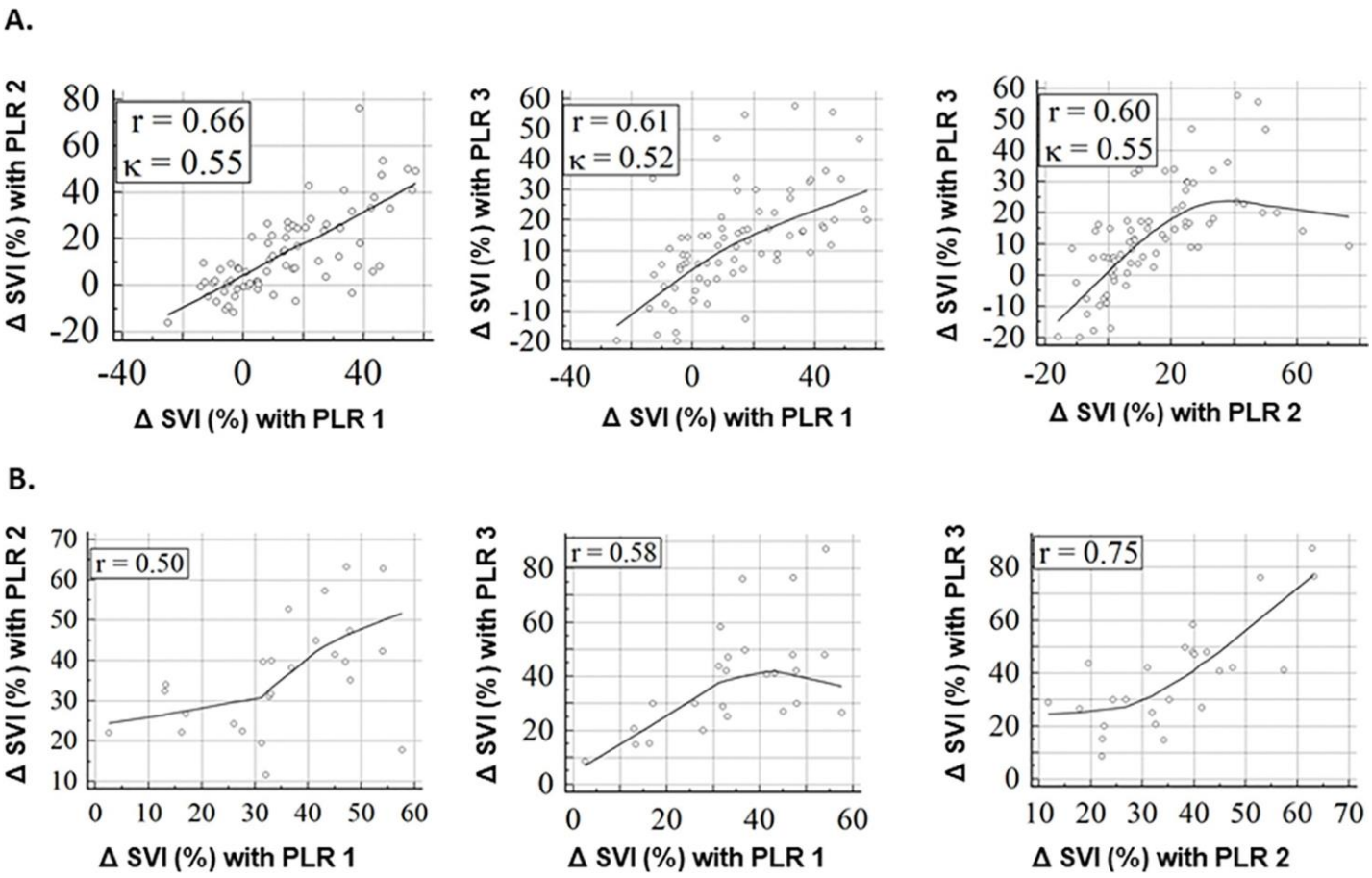

Fig 2. Correlation and agreement between cycles of passive leg raising (PLR) maneuvers. A. Patients. B. Volunteers. r–Pearson's correlation coefficients. K–Cohen's kappa for agreement in determining fluid responsiveness of "Yes" (ΔSVI > 10%) or "No" (ΔSVI 10%) between two PLR maneuvers. K was not calculated for volunteers since the consistency in determining fluid responsiveness over all three PLR maneuvers was 96.0% (Table 3).

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3. **Precision and consistency of passive leg raise in determining fluid responsiveness.** *Precision* is described by the range, average deviation, and standard deviation of the change in stroke volume index (ΔSVI) over 3 cycles of passive leg raising (PLR) maneuver. *Consistency* was defined as the same fluid responsiveness determination of "Yes" (ΔSVI > 10%) or "No" (ΔSVI 10%) over the 3 cycles of PLR maneuver. For example, a subject was categorized to have *consistent* results if they were persistently fluid responsive or not fluid responsive for all 3 cycles of PLR maneuver. A subject had *inconsistent* results if any one of the 3 cycles of PLR maneuver resulted in a fluid responsiveness determination that was different from the other PLR's. Data are represented as mean ± standard deviation or as count (percentage).

Precision	**Patients N = 75**	**Volunteers N = 25**	***p-value***
Range of ΔSVI (%)	17.2 ± 13.3	17.4 ± 10.3	0.94
Average deviation of ΔSVI (%)	6.5 ± 4.0	6.6 ± 3.8	0.91
Standard deviation of ΔSVI (%)	9.0 ± 5.2	9.0 ± 6.7	0.15
Consistency			
Consistent determination of fluid responsiveness	49 (65.3)	24 (96.0)	<0.01
Consistently fluid responsive with ΔSVI > 10%	24 (32.0)	24 (96.0)	<0.01

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Thus, the variability in ΔSVI after serial PLR's observed in our study may be contributed by inaccurate technology and/or clinically significant spontaneous changes in SV.

Lamia et al. further examined the accuracies of continuous CO measurements by various technologies incorporating arterial pulse contour analysis, bioreactance and thermodilution [19]. They found that compared to the pooled CO measured by all devices, the percentage error for CO was 34, 34, 49, 28 and 37% for LiDCO™ (LiDCO Ltd, London, UK), FloTrac™ (Edwards Life Science, Irvine, CA, USA), NiCOM™, PA catheter and PiCCO™ (Pulsion Ltd, Munich Germany), respectively. Thus, we posit that the variability in ΔSVI observed with NiCOM™ in our study will likely be similar with other technologies.

Our study showed that healthy volunteers were more fluid responsive than critically ill patients, with 96% of the volunteers being consistently fluid responsive with ΔSVI > 10%. Similarly, Miller et al. examined 40 healthy volunteers by performing the PLR followed by 500 mL intravenous bolus of 0.9% normal saline [20]. They showed that 90% of the subjects were fluid responsive. Kumar et al. also examined the hemodynamic responses to volume infusion in normal subjects using the PA catheter, and showed that 3 L of normal saline resulted in 30% increased CI and 23% increased SVI [21]. In our study, the hospital day at the time of enrollment was 5.0±5.6 days. Thus, many patients have already received some amount of fluid resuscitation, leading to less fluid responsiveness compared to volunteers.

We performed an observational study without a reference hemodynamic monitoring technology, such as the PA catheter, to compare the NiCOM™ against. We also did not confirm fluid responsiveness with administration of a fluid bolus. Recent systematic reviews already concluded that the PLR was the most accurate measure of fluid responsiveness compared to other modalities [5, 13]. Our aim was to determine the precision or repeatability of ΔSVI after PLR, and not its accuracy. Furthemore, fluid administration in between PLR's will change the patient's location on the Starling curve and invalidate the purpose of our study.

We did not have a priori estimate of the precision of ΔSVI after the PLR in the general population. Therefore, we could not perform a sample size calculation taking into consideration statistical vs. clinical significance. However, based on previous studies examining the accuracy of PLR, our study team arbitrarily agreed to enroll 75 critically ill patients and 25 healthy volunteers [13].

Previous studies examining the variability of CO have taken measurements at intervals of seconds to minutes [15, 16]. We used a pragmatic interval of 20–30 minutes allowing for data collection and subject repositioning in between consecutive PLR's. This longer interval may result in physiologic changes in CO and ΔSVI. However, we observed that SVI and CI did in fact return to baseline values during this interval. Additionally, it is not uncommon in

standard practice for volume assessment to be repeated at 20–30 minute intervals, rather than seconds or a few minutes, after an intervention.

1.12. Conclusion

In conclusion, our study showed the precision of determining ΔSVI by the NiCOM™ after the PLR is at ±9% in both critically ill patients and volunteers; however, consistency is significantly higher in volunteers. Although not tested, knowledge of precision and consistency of the PLR in predicting fluid responsiveness may impact clinical decision-making. The ΔSVI cutoff of 10% may need further clarification as 10±9%. With this level of variability, fluid responsiveness could perhaps be redefined as graded levels of responsiveness rather than as a binary prompt when utilizing non-invasive hemodynamic monitoring technologies. For example, ΔSVI < 5% may suggest "not fluid responsive", ΔSVI 5–15% suggests "possible fluid responsive", and ΔSVI > 15% "definitely fluid responsive". Further studies are thus needed to examine how precision of the PLR and such proposed modified definition of fluid responsiveness can be incorporated in fluid resuscitation protocols.

1.13. Supporting information

S1 File. Data set used to reach the conclusion drawn in the manuscript.
(XLSX)

1.14. Author Contributions

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Writing – review & editing: Jordan Thompson, Shahab Shahangian, Suman Thapamagar, Dafne Moretta, Chris Gasho, Avi Cohen, H. Bryant Nguyen.

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Original Article

Passive leg raising as an indicator of fluid responsiveness in patients with severe sepsis

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BACKGROUND: In the management of critically ill patients, the assessment of volume responsiveness and the decision to administer a fluid bolus constitute a common dilemma for physicians. Static indices of cardiac preload are poor predictors of volume responsiveness. Passive leg raising (PLR) mimics an endogenous volume expansion (VE) that can be used to predict fluid responsiveness. This study was to assess the changes in stroke volume index (SVI) induced by PLR as an indicator of fl uid responsiveness in mechanically ventilated patients with severe sepsis.

METHODS: This was a prospective study. Thirty-two mechanically ventilated patients with severe sepsis were admitted for VE in ICU of the First Affi liated Hospital, Zhejiang University School of Medicine and Ningbo Medical Treatment Center Lihuili Hospital from May 2010 to December 2011. Patients with non-sinus rhythm or arrhythmia, parturients, and amputation of the lower limbs were excluded. Measurements of SVI were obtained in a semi-recumbent position (baseline) and during PLR by the technique of pulse indicator continuous cardiac output (PiCCO) system prior to VE. Measurements were repeated after VE (500 mL 6% hydroxyethyl starch infusion within 30 minutes) to classify patients as either volume responders or non-responders based on their changes in stroke volume index (ΔSVI) over 15%. Heart rate (HR), systolic artery blood pressure (ABPs), diastolic artery blood pressure (ABPd), mean arterial blood pressure (ABPm), mean central venous pressure (CVPm) and cardiac index (CI) were compared between the two groups. The changes of ABPs, ABPm, CVPm, and SVI after PLR and VE were compared with the indices at the baseline. The ROC curve was drawn to evaluate the value of ΔSVI and the change of CVPm (ΔCVPm) in predicting volume responsiveness. SPSS 17.0 software was used for statistical analysis.

RESULTS: Among the 32 patients, 22 were responders and 10 were non-responders. After PLR among the responders, some hemodynamic variables (including ABPs, ABPd, ABPm and CVPm) were significantly elevated (101.2±17.6 vs.118.6±23.7, P=0.03; 52.8±10.7 vs. 64.8±10.7, P=0.006; 68.3±11.7 vs. 81.9±14.4, P=0.008; 6.8±3.2 vs. 11.9±4.0, P=0.001). After PLR, the area under curve (AUC) and the ROC curve of ΔSVI and ΔCVPm for predicting the responsiveness after VE were 0.882±0.061 (95%CI 0.759–1.000) and 0.805±0.079 (95%CI 0.650–0.959) when the cut-off levels of ΔSVI and ΔCVPm were 8.8% and 12.7%, the sensitivities were 72.7% and 72.7%, and the specifi cities were 80% and 80%.

CONCLUSION: Changes in ΔSVI and ΔCVPm induced by PLR are accurate indices for predicting fl uid responsiveness in mechanically ventilated patients with severe sepsis.

KEY WORDS: Passive leg raising; Volume resuscitation; Hemodynamic monitoring; Stroke volume index; Central venous pressure; Severe sepsis; Fluid responsiveness; ROC curve

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INTRODUCTION

In critically ill patients with hypoperfusion, intravascular volume expansion (VE) is a cornerstone of hemodynamic therapy. Early resuscitation protocols including fluid therapy can be life-saving early in the course of sepsis.[1,2] However, VE may induce peripheral and pulmonary edema, and worsen microvascular perfusion and oxygen delivery in patients with right or left ventricular dysfunction.[3] In a preload unresponsive patient, large VE can exacerbate pulmonary edema, cause respiratory failure, prolong mechanical ventilation time, and contribute to the development of intra-abdominal hypertension.[4] Passive leg raising (PLR) was supposed to transfer venous blood from the legs toward the intrathoracic compartment, increasing the intrathoracic blood volume and the cardiac preload. The aim of the present study was to determine if SVI measurement could be used in conjunction with PLR to predict the hemodynamic response to VE.

METHODS

1.16. Patients

This study prospectively assessed consecutive patients admitted in the ICU (33 beds) of the First Affiliated Hospital, Zhejiang University School of Medicine and the ICU (26 beds) of Ningbo Medical Treatment Center Lihuili Hospital from May 2010 to December 2011. Thirty-two mechanically ventilated patients, defined septic chock[5] with acute circulatory failure, were eligible to participate in the study with written informed consent. Hemodynamic indices including SVI were monitored with the technique of pulse indicator continuous cardiac output (PiCCO) (Pulsion Medical Systems AG, Munich, Germany). Acute circulatory failure was defined as the presence of at least one clinical sign of inadequate tissue perfusion as follows: systolic blood pressure<90 mmHg (or a decrease of >40 mmHg in previously hypertensive patients) or the need for vasopressors (dopamine>5 μg/kg per minute or norepinephrine>0.1 μg/kg per minute) to maintain a systolic blood pressure>90 mmHg; urine output of <0.5 mL/kg per hour for at least 1 hour; tachycardia (heart rate>100/min); and mottled skin.[6] Non-sinus rhythm or arrhythmia ones and parturients were excluded.

1.17. Mechanical ventilation variables

The patients were sedated (Ramsay score 4) and ventilated in mode of volume control. The tidal volume was 10 mL/kg and the level of positive end-expiratory pressure was 5 cmH_2O (1 cmH_2O=0.098 kPa).

1.18. Measurements

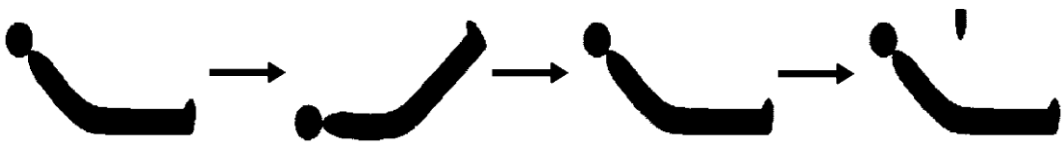
A 4F thermistor-tipped arterial catheter (Pulsiocath thermodilution catheter; Pulsion Medical Systems, Munich, Germany) was inserted in the femoral artery, which connected to the PiCCO (Pulsion Medical Systems, Munich, Germany) and the bedside monitor (IntelliVue MP50/70: Philips Medical System, Boeblingen, Germany).

Hemodynamic indices were determined using a triplicate injection of 15 mL ice-cold normal saline within 5 minutes through an additional 7 F central venous catheter introduced in the right subclavian vein. The bolus thermodilution measurements were made by the same observer to avoid interobserver variation.

1.19. Data collection

Study measurements were taken in four stages (Figure 1). In stage one, the patient was placed in a semi-recumbent position with the head elevated at 45 degrees, and hemodynamic indices were collected as the baseline. In stage two, the patient was placed in a supine position with the legs straight and elevated at 45 degrees for two minutes before hemodynamic indices were taken. In stage three, the patient was returned to the baseline position. In stage four, hemodynamic indices were immediately collected after VE (500 mL 6% hydroxyethyl starch infusion within 30 minutes).

Calibrated automatic bed elevation (using standard ICU beds) was used to move the patient between stages. Vasopressor doses and ventilator settings were not changed at any time while a patient was being studied. Patients were classifi ed according to their hemodynamic response to VE. Responders were defined as the change of SVI (ΔSVI) not less than 15% in response to VE (ΔSVI from stage one to stage four), while nonresponders were defined as ΔSVI less than 15%. A cutoff value of 15% was reported as a signifi cant difference by thermodilution.[7]



Stage 1: Head elevated at 45 degrees for 2 minutes before obtaining indices. Stage 2: Supine position with the legs elevated at 45 degrees for 2 minutes after VE in the baseline position. Stage 3: Baseline indices were collected as the baseline. Stage 4: Hemodynamic indices were collected before obtaining the position.

Figure 1. Patient position in the four stages of measurement.

1.20. Statistical analysis

$P<0.05$ was considered statistically signifi cant. Statistical analysis was performed using SPSS 17.0 software (SPSS, Chicago, IL) for all tests.

Parameters	HR	Responders	Non-responders	F		P v
(beats/min)		88.5±24.4	111.8±17.9	0.58		0.0
ABPs (mmHg)		101.2±17.6	118.6±23.7	0.37	0.19	0.0
ABPd (mmHg)		52.8±10.7	64.8±10.7	0.02		0.0
ABPm (mmHg)		68.3±11.7	81.9±14.4	1.40	4.40	0.0
CVPm (mmHg)		6.8±3.2	11.9±4.0		2.38	0.0
SVI (ml/m²)		33.4±8.1	35.3±13.3	0.02		0.0
CI (L/min/m²)		2.9±0.9	3.8±1.2	0.10		0.6
SVRI (DSm²/cm⁵	)	1799.1±590.1	1611.8±598.1	1.97		0.0
EVLWI	(ml/kg)	10.3±5.4	8.3±4.8			0.4
ITBVI (ml/m²)		912.0±188.2	841.8±153.9			0.3
						0.3

RESULTS

Clinical data

Thirty two patients, 11 females21 (65.6%) patients,

* ** *P*< 0.05, *P*< 0.01.

Parameters	All patients	Responders	Non-responders	*P* value
Age (yr)	59.4±14.2	60.1±16.1	57.9±10.1	0.33
Sex (*n*, %)				
Male	21 (65.6%)	15 (46.9%) 7 (21.8%)	6 (18.8%)	0.65
Female	11 (34.4%)	22.6±3.3	4 (12.5%)	
BMI (kg/m^2)	22.8±3.1	10.7±8.7	23.2±2.1	0.31
ICU admission (d)	10.8±9.3	10.5±7.6	11.0±10.4	0.95
Mechanical ventilator (d)	10.6±8.4	20.1±9.2	10.8±10.1 21.1±8.9	0.96
APACHE II score	20.4±8.8	9 (42.9%)	4 (40.0%)	0.57
In-hospital mortality (*n*, %)	13 (40.6%)			0.96

Numerical data were expressed as mean±SD. Responder and nonresponder values were compared using an independent-sample Student's *t* test. The values before and after PLR, before and after VE, and between stage 2 and stage 4 were compared using a paired-sample Student's *t* test. Qualitative variables were reported as number and percentage and compared between the groups using Fisher's exact test. The receiver-operating characteristic curves±SE were compared using the Hanley-McNeil test. Cut-off values for ΔSVI and for the change of CVPm (ΔCVPm) were chosen to correspond to the best respective Youden's index calculated as follows: Youden's index=sensitivity+specificity-1. Threshold indicator values such as sensitivity and specificity were calculated for each hemodynamic indicator tested. A bloodstream infection in 7 (21.9%), and abdominal infection in 4 (12.5%). ΔSVI increased by 15% or more in 22 (68.8%) patients (responders), and by less than 15% in 10 (31.2%) patients (non-responders). No statistical difference was found between responders and non-responders for age, sex, body mass index (BMI), days of ICU admission, days of mechanical ventilation, APACHEII scores and mortality (Table 1).

1.21. Baseline data

The responders had significantly lower initial HR, ABPs, ABPd, ABPm, CVPm and CI compared with the non-responders at the baseline (P<0.05) (Table 2).

1.22. Differences between the two groups

Changes in ABPs, ABPd, ABPm, CVPm and SVI compared with stage one induced by PLR and VE were significantly higher in the responders than in the nonresponders (P<0.05). In the non-responders, neither PLR nor VE induced a significant change in any of the hemodynamic values measured (Table 3).

1.23. ROC curve

The ΔSVI of 8.8% predicted fluid responsiveness with a sensitivity of 72.7% and a specificity of 80%,

Table 2. Initial hemodynamic readings taken in stage one

Table 3. Hemodynamic indices taken throughout the four stages of measurement

Parameters	Stage 1	Stage 2	$P_{(2,1)}$	Stage 4	$P_{(4,1)}$	$P_{(4,2)}$
Responders						
HR (beats/min)	88.5±24.4	87.1±23.8	0.86	86.0±19.1	0.71	0.86
ABPs (mmHg)	101.2±17.6	117.0±13.1	0.002**	126.1±7.8	0**	0.007**
ABPd (mmHg)	52.8±10.7	59.8±11.8	0.04*	63.5±11.5	0.003**	0.30
ABPm (mmHg)	68.3±11.7	77.9±12.1	0.01*	83.5±10.7	0**	0.11
CVPm (mmHg)	6.8±3.2	9.4±3.9	0.02*	10.0±3.3	0.002**	0.56
SVI (ml/m^2)	33.4±8.1	39.0±9.5	0.04*	42.2±12.2	0.007**	0.34
CI (L/min/m^2)	2.9±0.9	3.3±1.0	0.15	3.5±1.1	0.04*	0.44
SVRI (DSm^2/cm^5)	1799.1±590.1	1764.2±522.4	0.84	1789.8±564.9	0.96	0.88
EVLWI (ml/kg)	10.4±5.4	9.8±5.6	0.73	11.1±5.3	0.65	0.43
ITBVI (ml/m^2)	912.0±188.2	1021.7±206.4	0.07	1036.5±196.9	0.04*	0.81
Non-responders						
HR (beats/min)	111.8±17.9	114.9±16.3	0.69	110.6±17.0	0.88	0.57
ABPs (mmHg)	118.6±23.7	124.7±25.8	0.59	124.7±24.2	0.58	1
ABPd (mmHg)	64.8±10.7	70.3±14.7	0.35	68.8±14.6	0.49	0.82
ABPm (mmHg)	81.9±14.4	87.6±16.6	0.42	86.7±15.4	0.48	0.9
CVPm (mmHg)	11.9±4.0	13.3±5.1	0.5	14.2±3.7	0.2	0.65
SVI (ml/m^2)	35.3±13.3	36.1±12.7	0.89	37.7±13.3	0.69	0.79
CI (L/min/m^2)	3.8±1.2	4.1±1.3	0.67	4.1±1.5	0.63	0.93
SVRI (DSm^2/cm^5)	1611.8±598.1	1606.7±600.0	0.99	1561.6±547.8	0.85	0.86
EVLWI (ml/kg)	8.3±4.8	7.8±3.6	0.76	8.2±3.7	0.93	0.8
ITBVI (ml/m^2)	841.8±153.9	877.6±163.9	0.62	888.0±153.2	0.51	0.89

* **

$P<0.05$, $P<0.01$; $P_{(2,1)}$: stage 2 vs. stage 1; $P_{(4,1)}$: stage 4 vs. stage 1; $P_{(4,2)}$: stage 4 vs. stage 2.

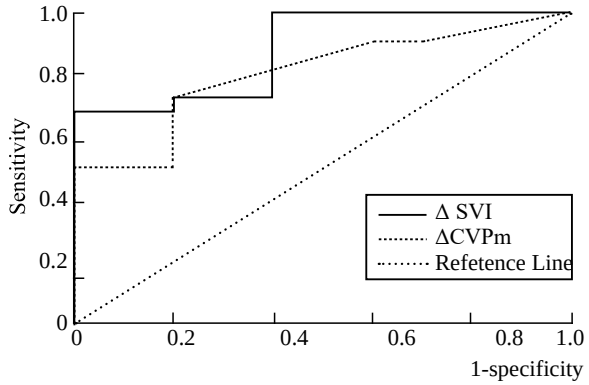


Figure 2. Receiver-operating characteristic curves comparing the capacity of changes induced by passive leg raising in ΔSVI and ΔCVPm to discriminate responders and non-responders regarding volume expansion in the overall population.

AUC (mean±SE)=0.882±0.061 (95%CI 0.759– 1.000); whereas the ΔCVPm of 12.7% predicted fluid responsiveness with a sensitivity of 72.7% and a specificity of 80%, AUC (mean±SE)=0.805±0.079 (95%CI 0.650–0.959) (Figure 2).

1.24. DISCUSSION

Blood volume plays an important role in the hemodynamic stability, which determines oxygen supplied to the tissues. Rapid infusion of crystalloids or colloids is the usual treatment for symptomatic hypovolemia.[8] Because VE does not always improve hemodynamic status, predictive parameters of fluid responsiveness are greatly needed. Blood volume is difficult to be measured at the bedside, so clinicians need to know whether left ventricular SVI increases after VE.[9] A simple, non-invasive bedside test for volume responsiveness determination which could assist clinicians in facing this daily dilemma might be of signifi cant use.

PLR is a reversible maneuver that mimics rapid VE by shifting venous blood from the lower limbs toward the intrathoracic compartment.[10] The classic lower limb raising mimics a 300 mL VE.[11] Given that trunk lowering may induce a 150 mL increase in intrathoracic blood volume,[12] we suggest that the PLR maneuver used in our study may mimic a VE of approximately 450 mL. Thus, PLR increases the cardiac preload and, by definition increases SVI if the heart is preloaddependent. However, the effects of PLR on cardiac output are variable, probably depending on the degree of the existence of cardiac preload dependence.[13] The responders in the study had significantly lower initial HR, ABPs, ABPd, ABPm, CVPm and CI compared with the non-responders. This suggested that the preload of the responders at the baseline was lower than that of the non-responders. After PLR, the indices including ABPs, ABPd, ABPm, CVPm and SVI elevated in the responders (P<0.05) as the consequences after VE. While the indices mentioned were not different between baseline and after PLR or between baseline and after VE in the non-responders (P>0.05) . The study demonstrated that a convenient ΔSVI measurement in conjunction with PLR could predict the hemodynamic response to VE. Changes in hemodynamic parameters such as SVI induced by PLR are accurate and interchangeable indices for predicting fl uid responsiveness in non-intubated critically ill patients.[7,8,14] The changes in ΔSVI and ΔCVPm induced by PLR were also proved to be predictive of fluid responsiveness in ventilated septic shock patients in the study. When mechanical ventilation is proceeding, the volume of blood enclosed by the thoracic and splanchnic beds is stressed by positive airway pressure, and these vascular compartments are less compliant than when mechanical ventilation is not required. In these conditions, the increase in ΔSVI induced by PLR was expected to be higher in mechanically ventilated patients than in non-intubated patients. So, PLR is a reversible maneuver that mimics rapid VE which might be widely used to evaluate the hemodynamic changes.[13]

The usual static hemodynamic parameters are not reliable indexes of the cardiac preload, so VE with invasive measurement of cardiac output is widely used to detect cardiac preload dependence which may result in worsening pulmonary edema. The dilemma of which patients are subject to VE is encountered daily in the ICU. One of the principal uses for the pulmonary artery catheter (PAC) was to differentiate between

various etiologies of hypotension and thereby guide therapy to optimize the hemodynamic status of a patient. However, with numerous clinical trials showing no benefit and concerns about safety, PAC is being used infrequently now in North American ICUs.[15] Transpulmonary thermodilution integrated in the PiCCO system does not require PAC placement and thus avoids the related risks, so it has been widely used for hemodynamic monitoring. Many physicians regarded CVP as a poor predictor of volume responsiveness and should not be used to make clinical decisions on fluid management.[16] But ΔCVPm induced by PLR was proved to be predictive of fluid responsiveness in this study. It suggested that dynamic changes in CVPm induced by PLR were more predictive of the preload than those static indicators on condition that the intrathoracic pressure, intra-abdominal pressure and ventricular compliance remaining unchanged. Thus the dynamic changes in CVPm induced by PLR provide a new method in preload estimation for wards without the condition of hemodynamic monitoring.

Sebastien et al[8] reported that SVI, measured by transthoracic echocardiography in conjunction with PLR, was an accurate index of fluid responsiveness by the research of the non-intubated septic shock patients. And ΔSVI>10% predicted fluid responsiveness with a sensitivity of 86% and a specifi city of 90%. Lafanechère and colleagues[17] examined 22 intubated and fully sedated patients with an esophageal Doppler monitor in place. An increase in aortic blood fl ow of more than 8% during PLR predicted volume response with a sensitivity of 90% and a specifi city of 83%, somewhat higher than the sensitivity and specificity in this study. It might be due to the measurement of PiCCO. But the feasibility of transthoracic echocardiography is variable which depends on hospital equipment, patient echogenicity, and physicians' skills. However, use of the PiCCO method to manage critically ill patients has been proved to decrease the need for vasopressors and mechanical ventilation despite a larger infused volume.[18] The advantage of PiCCO method is that it can be conveniently used to predict the volume responsiveness in conjunction with PLR in intubated patients with septic shock.

Catecholamines with α-adrenergic properties, by their venous vasoconstrictor effects, could have affected the results. They might have shifted venous blood from an unstressed to a stressed volume and might have amplified the preload augmentation effect of PLR in the patients. However, this phenomenon did not affect the interpretation of the results since the dosages of the catecholamines kept unchanged during the study.

The results of this study suggest that in septic shock patients receiving mechanical ventilation, the hemodynamic response to VE could be predicted by simply measuring ΔCVPm and ΔSVI in conjunction with PLR. It may have two practical implications: the existence of a cardiac preload dependence could be detected without the use of a PAC; and a potentially harmful fl uid-loading procedure could be avoided when unnecessary.

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Ethical approval: The study was approved by the Ethical Committee of Ningbo Medical Treatment Center Lihuili Hospital and the First Affiliated Hospital, Zhejiang University School of Medicine.

Confl icts of interest: There are no competing interests involving this study.

Contributors: Dong ZZ proposed and wrote the paper. Zheng X and Shi H provided technical support. All authors approved the fi nal version.

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The reliability and validity of passive leg raise and fluid bolus to assess fluid responsiveness in spontaneously breathing emergency department patients☆☆

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Keywords:
Fluid resuscitation
Noninvasive monitoring
Passive leg raise
Fluid bolus
Fluid responsiveness

Purpose: We investigated the reproducibility of passive leg raise (PLR) and fluid bolus (BOLUS) using the Non
Output Monitor (NICOM; Cheetah Medical, Tel Aviv, Israel) for assessment of fluid responsiveness (FR) in spo
breathing emergency department (ED) patients.
Methods: Prospective, observational study of a convenience sample of adult ED patients receiving intravenou
We assessed stroke volume (SV) using NICOM and obtained results from PLR, where the head of the bed was
semirecumbent to supine while the patients' legs raised to 45° for 3 minutes. Fluid bolus was defined as 5 m
saline infusion. Maximal increase in SV was recorded. Fluid responsiveness was defined as an increase of SV
10% from baseline. We obtained 4 consecutive responses for each patient; PLR1, PLR2, BOLUS1 separated ea
minutes, and BOLUS2 initiated immediately after the end of BOLUS1. We calculated κ statistics, correlation c
odds ratios with 95% confidence interval and Bland-Altman plots.
Results: We enrolled 109 patients enrolled in this study. The 2 PLRs were significantly correlated (r = 0.78, P
0.46 for FR (Pb .001). The 2 BOLUSES less strongly correlated (r = 0.14, P = .001) and κ = 0.06 for FR (P b .001
were responsive to PLR1 had 9.5 (3.6-25) odds of being FR for PLR2, whereas those responsive to BOLUS1 ha
4.3) increased odds of FR for BOLUS2.
Conclusion: In conclusion, we have found PLR as measured by the NICOM to be a promising tool for the eval
responsiveness. It was feasible for use in the ED, and the data suggest that the PLR technique may be more r
than the fluid bolus technique for assessing volume responsiveness.

article info abstract

1. Introduction

The primary goal of volume resuscitation is to increase stroke volume (SV) to increase oxygen delivery. Despite technological advances, fluid status assessment in the emergency department (ED) relies primarily on bedside judgment using clinical parameters such as pulse, blood pressure, and urine output. These criteria are all time insensitive and relatively poor indicators of fluid status [1]. Fluid administration requires careful monitoring because both inadequate fluids and fluid overload may worsen outcome [2,3].

Two common methods of providing preload increases to assess responsiveness are fluid boluses or passive leg raise (PLR) [4,5]. The fluid bolus technique is performed by giving a "test bolus" of intravenous (IV) fluids to determine if the heart's SV will increase in response to an increase in preload. If the SV increases during a volume challenge, then physiologically the patient may be classified as being on the ascending part of the Starling curve and will likely further increase SV (and subsequent oxygen delivery) in

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response to additional IV fluids. Conversely, if the patient is not responsive (does not increase their SV) to a volume challenge, then one may assume that further fluids will not achieve the desired result of increased SV and subsequent cardiac output or oxygen delivery. An alternative method to assess volume responsiveness is to perform a PLR (shift patient position from semirecumbent to a supine position while raising legs to 45°), which returns an estimated 300 cc of blood from the lower extremities to the heart, functioning as an endogenous, reversible preload challenge.

There are several challenges in monitoring patients in the ED because of fast turnover, patient mobility, and the impracticality of invasive monitoring due to the potential adverse effects. There are a number of devices and methods currently available to monitor fluid responsiveness (FR); however transesophageal echocardiography and transthoracic echocardiography are limited by the high user dependency and noncontinuous nature that requires frequent reassessments, whereas more traditional measures like central venous pressure and pulmonary artery occlusion pressures are time consuming, are invasive, and have questionable accuracy [6,7]. The FloTracVigileo^{TM} (Edwards Lifesciences, Irvine, CA, USA), LiDCO (LiDCO Ltd, London, UK), and PiCCO (Pulsion Medical Systems, Munich, Germany) are minimally invasive options that provide user independent continuous dynamic cardiac assessments [8,9]. The Non-Invasive Cardiac Output Monitor (NICOM; Cheetah Medical, Tel Aviv, Israel) is a noninvasive method that provides similar assessments and has shown good results in previous trials [10–12]. Given the potential constraints of the ED setting, we chose the NICOM as our monitoring tool because of feasibility considerations and ease of use in the ED [13,14].

Although studied relatively often in the intensive care unit (ICU), typically in intubated patients, PLR and FR methodologies are relatively less well studiedin the ED setting, especially in spontaneously breathing patients [15–17]. Furthermore, we are unaware of a previous investigation that compares reproducibility and accuracy of the 2 techniques of PLR and fluid boluses. The objective of this study is to determine the reproducibility and predictive accuracy of the PLR maneuver and fluid bolus techniques using the NICOM device to monitor FR in a heterogeneous group of ED patients receiving volume resuscitation.

2. Methods and materials

2.1 Study design and population

This was a prospective, observational cohort study of a convenience sample of adult ED patients (age, 18 years or older) who were prescribed IV fluids by the clinical team. Inclusion criteria are as follows:

1. Age N18 years
2. Clinical team intended to administer IV fluid (of at least 5 mL/kg) as part of treatment

Exclusion criteria are as follows:

1. Acuity precluding participation in research
2. Inability to perform a PLR (eg, lower extremity amputee patients) 3. Inability to obtain consent

Our local institutional review board approved the study, and a verbal informed consent was obtained from each patient before initiating the study.

2.2. Demographics and clinical covariates

We collected demographic variables (age, sex, and race), comorbid disease (chronic obstructive pulmonary disease, chronic heart failure, hypertension, peripheral vascular disease, valvular heart disease, diabetes, coronary artery disease), vital sign information (temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation), the result of laboratory testing (serum lactate, complete blood count, and chemistry panels), and patients' chief complaint, length of stay, and mortality.

2.3. NICOM assessment

All patients were instrumented with the NICOM, which consists of 4 stickers akin to electrocardiogram electrodes being attached to the thorax. The SV is calculated based on an analysis of relative phase shifts and amplitude changes of an oscillating current that passes between the sensors. The phase shifts and amplitude changes are highly correlated with aortic blood volume, thus representing the SV of the heart [14,18]. We performed a PLR and a bolus challenge for all patients. Both tests were performed using the preinstalled programs embedded in the NICOMdevice. For either test, the baseline consists of placing thepatient in a semirecumbent position (head of bed at 45°) for 3 consecutively recorded minutes. For the challenge stage of PLR, the head of the bed was lowered to a supine position and the patient's legs elevated to 45° for 3 minutes (Fig. 1). This maneuver transfers the blood trapped in the lower limbs centrally and increases the preload of the heart similar to a fluid bolus estimated at 300 mL [19]. The fluid bolus test consisted of an infusion of 5 cc/kg crystalloids. The patient remained in a semirecumbent position during fluid infusion. Four consecutive measurements with the NICOM were performed and labeled: PLR1, PLR2, BOLUS1, and BOLUS2. BetweenPLR1,PLR2,andBOLUS1,therewasa 10-minutepause before the next sequence was started to allow the SV to return to baseline; that is, displaced central blood volume returns to lower limbs. BOLUS2 was initiated immediately after the end of BOLUS1 (Fig. 2).

2.4. Outcomes

Fluid responsiveness was defined a priori as an increase in SV greater than 10% from the prechallenge baseline for that particular maneuver. Absolute values of SV were collected for both the prechallenge and challenge stages.

2.5. Data analysis

Means with SDs, medians with interquartile ranges, and proportions were used for descriptive statistics, as appropriate. All test results were analyzed both in a continuous and in a categorical manner. For the categorical analysis, patients were categorized as fluid responsive or nonresponsive with FR defined as an SV increase of 10% or more. For continuous data, we used a Pearson correlation coefficient to define the degree of responsiveness between PLR1 and PLR2 as well as between BOLUS1 and BOLUS2. For agreement between categorical variables, we calculated a Cohen κ. We also constructed 2 ×2 tables for PLR1 vs PLR2, PLR2 vs BOLUS1, and BOLUS1 vs BOLUS2; calculated the odds ratios and κ value, along with 95% confidence intervals and Bland-Altman plots; and report the average bias and limits of agreement.

2.6. Sample size assessment

To determine whether passive leg raising and fluid boluses are at least 65% sensitive and specific in detecting a 10% increase in SV, we assumed that the prevalence of responsiveness is 50%. With a point estimate of 80% for both sensitivity and specificity, we estimated that a minimum of 88 patients are required to ensure enough power for the lower bounds of the 95% confidence interval to be above 65%. We

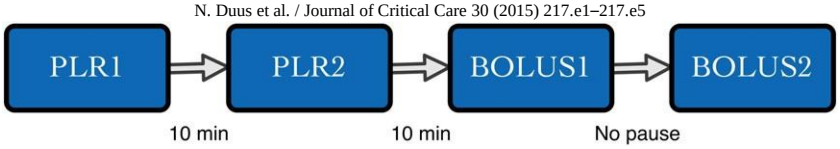

Fig. 2. Flowchart of the consecutive measurements.

Fig. 1. Illustration of the PLR maneuver.

observed additional variability during the study, so we increased our power by enrolling an additional 21 patients.

3. Results

3.1. Patient characteristics

We enrolled a total of 109 patients in the study with, a mean (SD) age of 49 (18) years; 69% were female and 74% were white (Table 1). The most frequent chief complaints were as follows: abdominal pain (42%), nausea/vomiting/diarrhea (17%), and infection (4%). Fortythree percent of the patients enrolled were later admitted to the hospital; 2 died. The mean lactate was 1.4 and Acute Physiology and Chronic Health Evaluation II score was 5, both indicating a relatively noncritically ill population. None of the patients enrolled were hemodynamically unstable upon enrollment. The average (SD) SV responsiveness for each maneuver was as follows: PLR1, 23% (0.2%); PLR2, 21% (0.2%); BOLUS1, 20% (0.2%); and BOLUS2, 12.5% (0.2%). The rate of responsiveness defined by an increase in SV greater than 10% was as follows: PLR1, 73%; PLR2, 66%; BOLUS1, 60%; and BOLUS2, 51%.

Table 1
Patient characteristics

Demographics	N=109
Age median, mean (SD)	49, 49 (18)
Race: White n (%)	74 (68%)
African-American	19 (17%)
Other	16 (15%)
Female gender n (%)	69 (63%)
Comorbidities n (%)	
COPD	1 (1%)
Chronic Heart Failure	3 (3%)
Hypertension	35 (32%)
Peripheral Vascular Disease	0 (0%)
Valvular Heart Disease	2 (2%)
Diabetes	27 (25%)
CAD	9 (8%)
Clinical Covariates median, mean (SD)	
Systolic Blood pressure	125, 126 (19)
Diastolic Blood Pressure	73, 73 (13)
Heart rate	80, 81 (15)
Temperature (Fahrenheit)	98.2, 98.4 (1.3)
Severity of Disease, median, mean (SD)	
APACHE II score	4, 5 (3.6)
Lactate (mg/dL)	1.3, 1.4 (0.6)
Chief complaint on admission n (%)	
Abdominal pain	42 (38%)
Flank Pain	5 (5%)
Infection	4 (4%)
Nausea, vomiting, diarrhea	17 (17%)
Other	41 (38%)
Biochemistry levels on admission, median, mean (SD)	
White blood cells	8.1, 8.8 (3.9)
Hematocrit	39.0, 39.1 (5.0)
Creatinine	0.8, 1.0 (0.6)

Sodium	138, 138 (4)
Potassium	4.0, 4.1 (0.7)
Admitted n (%)	47 (43%)
Length of stay, mean (days)	2.0
Mortality n (%)	2 (2%)

3.2. PLR1 vs PLR2 (105 data points)

The 2 PLRs were well correlated (r = 0.78, P b .001), with a κ for FR of 0.46 (P b .001; Table 2 and Fig. 3). Bland-Altman statistics showed that there was an average (SD) bias for PLR1 compared with PLR2 of 2.0% (11%), with the limits of agreement ranging from −23.5% to 19.6% (the range over which 95% of the differences between the PLRs will be contained; Fig. 4). Using PLR2 as criterion standard, the sensitivity of PLR1 in predicting FR to PLR2 was 0.88 (0.81-0.95) and the specificity was 0.56 (0.46-0.66), with an overall accuracy of 0.78 (0.7-0.86). Patients who were responsive to PLR1 had a 9.5 (3.6-25) increased odds of having a response to PLR2 as compared with nonresponders to PLR1. 3.3. PLR2 vs BOLUS1 (100 data points)

PLR2 and BOLUS1 had a κ for FR of 0.4 (P b .001; Table 3). Using BOLUS1 as criterion standard, the sensitivity of PLR2 in predicting FR to BOLUS1 was 0.80 (0.72-0.88) and the specificity was 0.61 (0.51-0.71), with an overall accuracy of 0.74 (0.65-0.83). Patients who were responsive to PLR2 had a 6.8 (2.7-17) increased odds of having a response to BOLUS1 as compared with nonresponders to PLR2.

3.4. BOLUS1 vs BOLUS2 (94 data points)

BOLUS 1 and BOLUS2 were not well correlated (r = 0.14) with a κ of 0.06 (P b .001; Table 4 and Fig. 5). Bland-Altman statistics showed that there was an average (SD) bias for BOLUS1 compared with BOLUS2 of −5.6% (18%), with the limits of agreement ranging from −40.6% to 29.4% (the range over which 95% of the differences between the BOLUSes will be contained; (Fig. 6). The operating characteristics of BOLUS1 in predicting FR to BOLUS2 demonstrated a sensitivity of 0.71 (0.62-0.8) and a specificity of 0.41 (0.31-0.51), with an overall accuracy of 0.60 (0.50-0.70). Patients who were responsive to BOLUS1 had a 1.82 (0.76-4.33) increased odds of having a response to BOLUS2 as compared with nonresponders to BOLUS1.

4. Discussion

In the present study, we found SV response to PLR as measured by the NICOM to be moderately reproducible and significant, whereas the fluid bolus technique was less

reproducible. These results suggest that the PLR-maneuver may be a more promising technique for assessing FR in spontaneously breathing ED patients. An important feature to PLR is the reversibility due to its endogenous nature; thus, fluid overloading can be avoided in nonresponsive individuals. This also provides an explanation to the lack of reproducibility for the bolus test; because preload is increased irreversibly, a subsequent test initiates from an entirely different baseline.

Table 2 κ Statistics for SV responsiveness to PLR1 and PLR2 (n = 105)

	PLR2	
	No response	Response
PLR1		
Response	19	9
No response	14	63

κ Statistics = 0.459. P b .001.

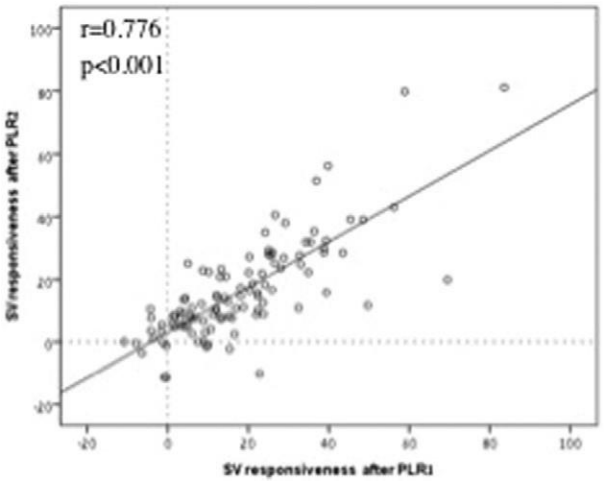

Fig. 3. Correlation between SV responsiveness to PLR1 and PLR2.

Passive leg raise assessment of response to fluid bolus has been investigated previously. These studies reported results with better operating characteristics for PLR predicting response to a bolus test. In 2010,Cavallaro et al[20]published a systematic review ofthe diagnostic accuracy of PLR for predicting FR in adult ICU patients. The review contained both studies in ventilated and nonventilated patients and patients with atrial fibrillation and sinus rhythm. They included 9 studies with a total of 353 patients, and 7 different methods were applied to measure response to PLR to predict the response to a fluid challenge. The overall sensitivity and specificity were 89.4% (84.1%93.4%)and 91.4% (85.9%-95.2%).Monge Garciaet al[21]investigated the correlation of PLR with infusion of 500 mL colloids administered for 30 minutes in 37 mechanically ventilated patients with acute circulatory failure using esophageal Doppler. They found a correlation of (R^2 = 0.79; P b .0001) and a sensitivity and specificity of 95.2% (76.2%-99.9%) and 93.7% (69.8%-99.8%). In 2010, Benomar et al [22] found a sensitivity of 68% and a specificity of 95% when assessing passive leg raising as a predictor for FR to a rapid infusion of 500 mL IV colloid bolus in 75 intubated patients immediately after cardiac surgery. In 2012,

Marik et al [23] found a sensitivity and specificity of 94% and 100% for passive leg raising in predicting response to a 500 mL NS bolus infused for 10 minutes using a pressure bag. The study included 34 hemodynamic unstable ICU patients, of which 19 were mechanically ventilated. Existing literature reports that an average around 50% of a study populationis fluid responsive. Inthe study byMariket al, 53%of patients

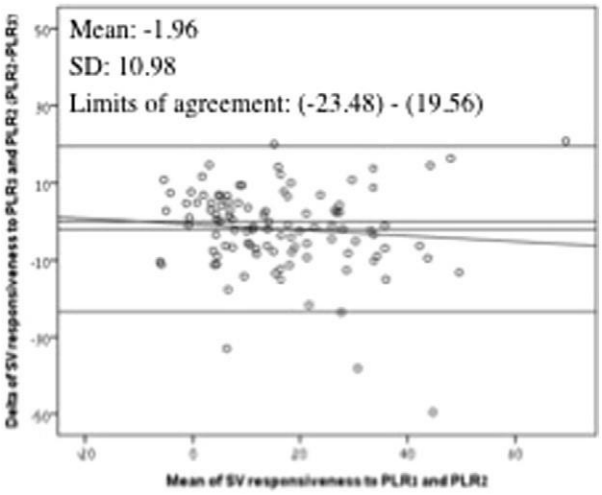

Fig. 4. Bland Altman Plot for SV responsiveness to PLR1 and PLR2.

Table 3 κ Statistics for SV responsiveness to PLR2 and BOLUS1 (n = 100)

	BOLUS1	
	No response	Response
PLR2		
No response	22	12
Response	14	52

κ statistics = 0.396. P b .001.

Table 4

κ Statistics for SV responsiveness to BOLUS1

	PLR2	
	No respone	Response
PLR1		
No response	16	16
Response	22	40

κ Statistics = 0.055. P b .001.

were responsive, 61% in the study by Benomar et al and 41% for Preau et al. Our data showed responsiveness in 74% of patients for PLR1. Our operating characteristics were clearly lower and less reliable than the findings of these studies.

4.1. Future directions

Based on the present study, our data suggest (but do not confirm) that the use of PLR may be a more promising maneuver for assessment of FR in ED patients. To further assess accuracy, studies comparing the accuracy of PLR vs

boluses as measured by other noninvasive tools other than the NICOM in the ED are warranted. To assess clinical use, randomized controlled trials of the potential impact of PLR response– directed fluid resuscitation on morbidity and mortality for selected groups of ED patients are needed to make a final determination. In addition, an important next study in the ED would be in the more critically ill, who are in need of aggressive resuscitation.

4.2. Limitations

A potential limitation is the observational design of the study with patients after their plan of action in regard to imaging, blood draws, and transfers, regardless of timing with the study. We did not control rate of infusion via pump, nor did we apply a pressure bag to ensure a rapid and uniform fluid infusion. Second, a possible source of error is whether 10 minutes between the 2 PLRs and bolus is a sufficient amount of time for

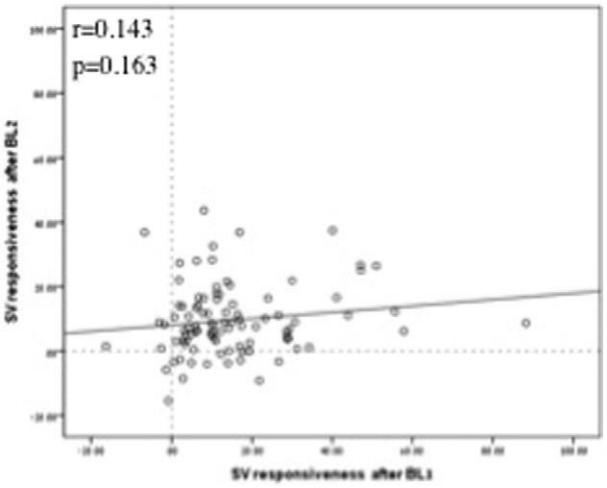

Fig. 5. Correlation between SV responsiveness to BL1 and BL2.

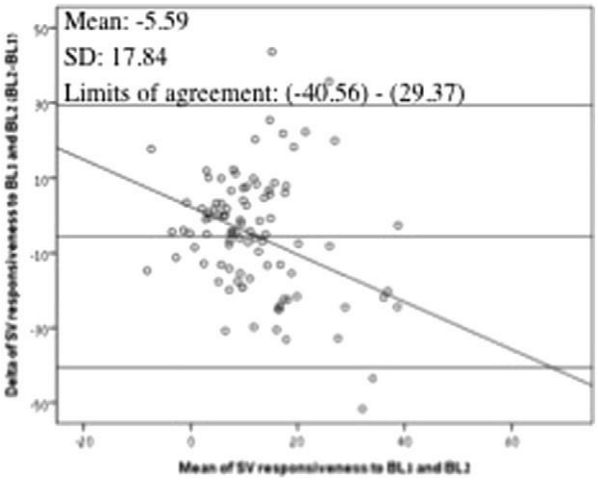

Fig. 6. Bland Altman Plot for SV responsiveness to BL1 and BL2.

the patient's SV to return to their baseline. Third, variability in patient's IVsizeand placementmadeinfusion ratesverydifferent. Fourth,a larger test bolus may improve accuracy. There may have been other unmeasured confounders that were not accounted for in the analysis. Fifth, this was a convenience sample of all patients presenting to the ED requiring IVfluids;specific populationsmay haverespondeddifferently. Sixth, our sample size could be expanded in future trials. Lastly, we did not use a criterion standard technique such as a Swan-Ganz catheter or another methodology to definitively assess accuracy.

5. Conclusion

In conclusion, we have found PLR as measured by the NICOM to be a promising tool for the evaluation of SV responsiveness. It was feasible for use in the ED, and the data suggest that the PLR technique may be more reproducible than the fluid bolus technique for assessing volume responsiveness. This is likely related either to a less reproducible fluid challenge or to the irreversible changes made by the first bolus, which, as expected, moved the patients upward the Starling curve, thus limiting the application to guide resuscitation. Future studies are needed using alternative criterion standard approaches to definitively assess the accuracy of the technique.

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Original Article

Effect of Systolic Cardiac Function on Passive Leg Raising for Predicting Fluid Responsiveness: A Prospective Observational Study

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Abstract

Background: Passive leg raising (PLR) represents a "self-volume expansion (VE)" that could predict fluid responsiveness, but the influence of systolic cardiac function on PLR has seldom been reported. This study aimed to investigate whether systolic cardiac function, estimated by the global ejection fraction (GEF) from transpulmonary-thermodilution, could influence the diagnostic value of PLR.

Methods: This prospective, observational study was carried out in the surgical Intensive Care Unit of the First Affiliated Hospital of Sun Yat-sen University from December 2013 to July 2015. Seventy-eight mechanically ventilated patients considered for VE were prospectively included and divided into a low-GEF (<20%) and a near-normal-GEF (≥20%) group. Within each group, baseline hemodynamics, after PLR and after VE (250 ml 5% albumin over 30 min), were recorded. PLR-induced hemodynamic changes (PLR-Δ) were calculated. Fluid responders were defined by a 15% increase of stroke volume (SV) after VE.

Results: Twenty-five out of 38 patients were responders in the GEF <20% group, compared to 26 out of 40 patients in the GEF ≥20% group. The thresholds of PLR-ΔSV and PLR-Δ cardiac output (PLR-ΔCO) for predicting fluid responsiveness were higher in the GEF ≥20% group than in the GEF <20% group (ΔSV: 12% vs. 8%; ΔCO: 7% vs. 6%), with increased sensitivity (ΔSV: 92% vs. 92%; ΔCO: 81% vs. 80%) and specificity (ΔSV: 86% vs. 70%; ΔCO: 86% vs. 77%), respectively. PLR-Δ heart rate could predict fluid responsiveness in the GEF ≥20% group with a threshold value of −5% (sensitivity 65%, specificity 93%) but could not in the GEF <20% group. The pressure index changes were poor predictors. **Conclusions:** In the critically ill patients on mechanical ventilation, the diagnostic value of PLR for predicting fluid responsiveness depends on cardiac systolic function. Thus, cardiac systolic function must be considered when using PLR.

Trial Registration: Chinese Clinical Trial Register, ChiCTR-OCH-13004027; http://www.chictr.org.cn/showproj.aspx?proj=5540.

Key words: Fluid Responsiveness; Passive Leg Raising; Systolic Cardiac Function; Volume Expansion

Introduction

Hypovolemia is a very frequent clinical situation in the Intensive Care Unit (ICU), for which the rapid fluid infusion is applied as treatment. Therefore, it is essential to have reliable tools to predict the efficacy of volume expansion (VE) and ultimately distinguish patients who may benefit from VE from those who are unlikely to respond. Recently, many studies have focused on the prediction of fluid responsiveness. Static hemodynamic indices have been of little value in predicting fluid responsiveness.[1,2] In contrast, dynamic indices, based on analysis of preload dependence, have been validated as factors that can help predict fluid responsiveness.[1,3-5] Passive leg raising (PLR) is a reversible maneuver that mimics rapid VE by shifting venous blood from the lower limbs[6] toward the intrathoracic compartment.[7,8] Thus, PLR increases the cardiac preload and, by definition, increases the stroke volume (SV) if the heart is preload dependent.[9-11] Recent studies demonstrated that PLR-induced changes in SV (PLR-ΔSV) and cardiac output (PLR-ΔCO) are reliable predictive indices of fluid responsiveness.[12-17] The fluid responsiveness describes the change of SV or cardiac output which varies with the preload basing on a Frank–Starling curve. However, patients with different cardiac functions show different Frank–Starling curves, especially for the patients with normal or low cardiac function. Therefore, it is not clear whether this will affect the prediction of fluid responsiveness or not, and the predictive value of PLR in patients with normal or low cardiac function has not been clearly established.

The aim of this study was to test whether systolic cardiac function can influence the diagnostic value of PLR in predicting fluid responsiveness.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (No. 2013-12-03). Informed written consent was obtained from all patients prior to their enrollment in this study.

Patients

This prospective, observational study (Chinese Clinical Trial Register: ChiCTR-OCH-13004027) was carried out in the surgical ICU of the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) from December 2013 to July 2015. The ventilated patients with presumed hypovolemia who received fluid expansion at the discretion of the attending physician were consecutively included. This decision was based on the presence of at least one clinical sign of inadequate tissue perfusion and the absence of contraindications for fluid infusion. Clinical signs of inadequate tissue perfusion were defined as follows: clinical signs of acute circulatory failure (systolic arterial pressure [SAP] <90 mmHg [or a decrease of <40 mmHg in previously hypertensive patients]; urine output of <0.5 ml·kg^{-1}·h^{-1} for at least 1 h; tachycardia [heart rate >100/min]; mottled skin), oliguria (diuresis below 20 ml/h or 0.5 ml·kg^{-1}·h^{-1}), acute kidney failure, and/or clinical and laboratory signs of extracellular dehydration.[16,17] Exclusion criteria included clinical signs of hemorrhage, inability to defer fluid challenge for several minutes, arrhythmia, moderate or severe valvular regurgitation, a contraindication to PLR, preterminal illness with a life expectancy of less than 24 h, or known anaphylactic reactions to albumin.

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Study design

Figure 1 illustrates the design of the study. Hemodynamics (heart rate [HR], SAP, mean arterial pressure [MAP], pulse pressure [PP], CO, and SV) were recorded at each step of the protocol. Baseline 1 indicates that patients were in a semi-recumbent position, with the trunk elevated 30–45° relative to the lower limbs. PLR indicates that patients were in a supine position with the lower limbs elevated 30–45° relative to the trunk. Each hemodynamic measurement was recorded within the first 5 min. PLR-induced changes (PLR-Δ) are expressed in percentages as follows: 100 × (PLR value − baseline 1 value)/baseline 1 value. Baseline 2 indicates that the lower limbs and trunk were returned to baseline 1 position for at least 5 min. After hemodynamic measurements, VE was performed within 30 min by infusing 250 ml 5% albumin. Post-VE indicates that after VE, patients remained in the baseline 2 position. VE-induced changes (VE-Δ) are expressed in percentages as follows: 100 × (post-VE value − baseline 2 value)/baseline 2 value. Patients were considered responders to VE if VE-ΔSV increased by 15%. The ventilation parameters and vasoactive drugs were maintained during the study.

Measurements

The following characteristics were recorded: age, gender, Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score, the use of vasoactive, sedative, and analgesic drugs, indication for ICU stay, and medical history.

We used the PiCCO system (Pulsion Medical System, Munich, Germany)[18,19] for hemodynamic monitoring. This device allows continuous measurement of the arterial pressure (SAP, diastolic arterial pressure [DAP], and MAP) and HR. PP was calculated as the SAP minus the DAP. The system uses a transpulmonary-thermodilution method for measurements of volume status (global end-diastolic volume [GEDV]). Additionally, this system also can provide information on cardiac function, including global ejection fraction (GEF),[20,21] cardiac function index (CFI),[20-22] and left ventricular contractility index (dp/dt max). These indicators can accurately reflect systolic cardiac function. A central venous catheter was inserted into the internal jugular vein or the subclavian vein, and a PiCCO arterial catheter was inserted into the femoral artery. Then, a series of three 15-ml ice-cold saline boluses at a temperature of <8°C were injected into the central vein, and the associated dilution curves and various hemodynamic parameters were obtained.[18] All patients received volume-controlled mechanical ventilation with positive end-expiratory pressure. Drainage of blood was <50 ml/h in all patients, and no patient underwent repeated surgery for bleeding within 12 h postsurgery.

Statistical analysis

The patients to be analyzed were divided into low-GEF (<20%) and near-normal-GEF (≥20%) groups. This cutoff of 20% reflects an approximate cutoff of 40% of the ejection fraction of the left ventricle, corresponding to the low limit of normal.[20,21,23] The Kolmogorov–Smirnov test was used to check the normality of the data distribution. All continuous variables were normally distributed and expressed as mean ± standard deviation (SD). Intergroup comparisons of continuous and categorical variables were performed with Student's *t*-test and the Chi-square test, respectively.

In each group, patients were classified as responders and nonresponders. Absolute values at baseline and during PLR and VE were analyzed. Comparisons before and after PLR, before and after VE, and between baseline 1 and baseline 2 were performed using a paired-sample Student's *t*-test. The comparison between responder and nonresponder values was performed using an independent-sample Student's *t*-test. The receiver-operating characteristic (ROC) curves were compared using the Hanley–McNeil test.[24] Cutoff values for ΔSV, ΔCO, ΔPP, ΔSAP, ΔMAP, and ΔHR were chosen to correspond to the best respective Youden's index[25] calculated as follows: Youden's index = sensitivity + specificity − 1. Threshold indicator values such as sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for each hemodynamic indicator tested. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 19.0 software (SPSS, Chicago, IL, USA) for all tests except the Hanley–McNeil test.

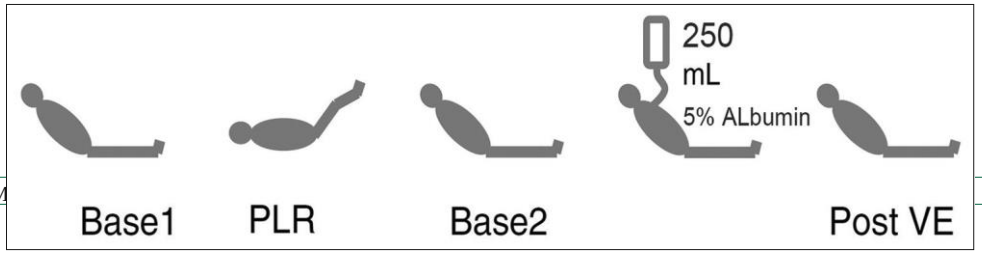

Figure 1: Study design. Base: Baseline; PLR: Passive leg raising; VE: Volume expansion.

Results

Patients' characteristics

A total of 78 ventilated patients with presumed hypovolemia and considered for VE were included in the study. Of these, 38 patients were assigned to the low-GEF group (<20%) and 40 patients were assigned to the near-normal-GEF group (≥20%). Table 1 summarizes the clinical characteristics, ventilation settings, and hemodynamics of the two patient groups. There were no significant differences between the two groups in terms of clinical characteristics. Cardiac function parameters were significantly higher in the near-normal-GEF group than in the low-GEF group. The ventilation settings, baseline volume status, and hemodynamics were similar between the two groups, with the exception of SV, CO, SAP, and PP, which were significantly higher in the near-normal-GEF group. Additionally, CVP was significantly lower in the near-normal-GEF group than in the low-GEF group.

Hemodynamic changes during passive leg raising and volume expansion

In the low-GEF (<20%) group, 25 patients were considered responders, with an increase in SV of 15% or more after VE. In the near-normal-GEF (≥20%) group, 26 patients were considered responders. The hemodynamic parameters at each step of the protocol (baseline 1, during PLR, baseline 2, and after VE) are shown in Table 2. Within each group, hemodynamic parameters were identical at baseline 1 and baseline 2. There were no significant differences between responders and nonresponders at baseline, with the exception of higher SAP/MAP values in nonresponders of the low-GEF group and higher CO/SV and lower PP in nonresponders of the near-normal-GEF group. After PLR and VE, the hemodynamic parameters showed significant changes in responders but not in nonresponders [Table 2]. Values of PLR-Δ are shown in Supplementary Table 1. All index changes in the near-normal-GEF group were significantly higher in responders than in nonresponders, except for PLR-ΔPP, while in the low-GEF group, only PLR-ΔSV and PLR-ΔCO were significantly higher in responders.

Correlations and receiver-operating characteristic curves

The correlation between PLR-Δ and VE-ΔSV is shown in Table 3. Regardless of GEF, PLR-ΔSV and PLR-ΔCO were positively correlated with VE-ΔSV. In addition, PLR-ΔHR was negatively correlated with VE-ΔSV in the near-normal-GEF (≥20%) group. None of the other variables were correlated with VE-ΔSV in either group. The areas under the ROC curves (AUC) for all index changes in the near-normal-GEF group were greater than the corresponding changes in the low-GEF group. The highest AUC values were for PLR-ΔSV (0.860 ± 0.059) and PLR-ΔCO (0.840 ± 0.063) in the low-GEF group and for PLR-ΔSV (0.942 ± 0.038) and PLR-ΔCO (0.859 ± 0.063) in the near-normal-GEF group [Table 3 and Figure 2].

Diagnostic performance of fluid responsiveness

In practical terms, the optimum threshold values and associated sensitivities and specificities for distinguishing fluid responders from nonresponders are presented in Table 3. In total, the index changes in the GEF ≥20% group showed better predicting ability than those in the GEF <20% group. The thresholds of PLR-ΔSV and PLR-ΔCO for predicting fluid responsiveness were higher in the GEF ≥20% group than in the GEF <20% group (ΔSV: 12% vs. 8%; ΔCO: 7% vs. 6%), with increased sensitivity (ΔSV: 92% vs. 92%; ΔCO: 81% vs. 80%) and specificity (ΔSV: 86% vs. 70%; ΔCO: 86% vs. 77%), respectively. Regarding PLR-ΔHR, this value could predict fluid responsiveness in the GEF ≥20% group, with a threshold value of −5% (sensitivity 65%, specificity 93%), but could not do so in the GEF <20% group. The other pressure index

Table 1: Descriptive characteristics of the mechanically ventilated patients considered for volume expansion

Characteristics	GEF <20% (*n* = 38)	GEF ≥20% (*n* = 40)	Statistics	*P*
Age (years)	64 ± 6	58 ± 14	2.019*	0.051
Male/female	27/11	32/8	0.847†	0.357
APACHE II score	17 ± 6	16 ± 6	0.818*	0.418
SOFA score	8 ± 5	6 ± 5	1.432*	0.159
Sedation and analgesics use/not use	29/9	26/14	1.200†	0.273
Vasoactive drug use/not use	31/7	34/6	0.164†	0.685
Surgical/nonsurgical admission	30/8	27/13	1.298†	0.255
Indication for ICU stay, *n* (%)				
Sepsis	35 (92)	34 (85)	0.964†	0.326
Pancreatitis	1 (3)	1 (2.5)	0.001†	0.971
Trauma	0 (0)	2 (5)	1.950†	0.163
SIRS without infection	2 (5)	3 (7.5)	0.163†	0.687
Medical history, *n* (%)				
Hypertension	11 (29)	6 (15)	2.224†	0.136
Diabetes mellitus	5 (13)	4 (10)	0.190†	0.663
COPD	8 (21)	6 (15)	0.485†	0.486
Ventilation				
Tidal volume (ml/kg)	7.8 ± 1.3	7.6 ± 1.9	0.383*	0.525
Plateau pressure (cmH_2O)	22.1 ± 3.3	20.8 ± 2.6	1.577*	0.122
PEEP (cmH_2O)	6.7 ± 2.6	6.0 ± 1.7	1.125*	0.267
Intra-abdominal pressure (cmH_2O)	12.2 ± 3.9	11.9 ± 3.4	0.288*	0.774
Cardiac function				
GEF (%)	12 ± 2	26 ± 3	−16.246*	0.000
dp/dt max (mmHg/s)	946 ± 390	1346 ± 357	−3.624*	0.001
CFI (L/min)	3.6 ± 0.8	7.4 ± 0.4	−19.363*	0.000
CPO (W)	0.31 ± 0.13	0.48 ± 0.15	−4.363*	0.000
Hemodynamics				
GEDV (ml)	737 ± 190	695 ± 103	0.912*	0.369
CVP (mmHg)	7 ± 1	5 ± 2	2.382*	0.023
Lac (mmol/L)	3.5 ± 2.8	3.3 ± 2.4	0.271*	0.788
HR (beats/min)	110 ± 11	110 ± 16	0.128*	0.899
SAP (mmHg)	98 ± 10	117 ± 14	−5.201*	0.000
DAP (mmHg)	57 ± 8	53 ± 12	1.485*	0.145
MAP (mmHg)	71 ± 8	74 ± 10	−1.157*	0.254
PP (mmHg)	41 ± 12	64 ± 16	−5.654*	0.000
SV (ml)	40 ± 15	61 ± 20	−4.002*	0.000
CO (L/min)	4.2 ± 1.4	6.6 ± 1.9	−4.761*	0.000

Values were shown as mean ± SD, *n*, or *n* (%). **t* values; †χ^2 values. GEF: Global ejection fraction; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Unit Care; SIRS: Systemic inflammatory response syndrome; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; PEEP: Positive end-expiratory pressure; CFI: Cardiac function index; CPO: Cardiac power output; GEDV: Global end-diastolic volume; CVP: Central venous pressure; Lac: Lactic acid; HR: Heart rate; SAP: Systolic arterial pressure; DAP: Diastolic arterial pressure; MAP: Mean arterial pressure; PP: Radial pulse pressure; SV: Stroke volume; CO: Cardiac output; SD: Standard deviation.

changes, ΔSAP, ΔMAP, and ΔPP, showed poor ability to predict fluid responsiveness [Table 3 and Figure 3].

1.26. dIscussIon

Our study suggests that the diagnostic value of PLR depends on the systolic cardiac function in ventilated patients in the ICU. PLR-ΔSV and PLR-ΔCO enabled

Table 2: Hemodynamic parameters at each step of the protocol in responders and nonresponders in each group

Parameters	GEF <20% (*n* = 38)		GEF ≥20% (*n* = 40)	
	Responders (*n* = 25)	Nonresponders (*n* = 13)	Responders (*n* = 26)	Nonresponders (*n* = 14)
SV (ml)				
Base 1	38 ± 17	47 ± 10	51 ± 12*	79 ± 21
PLR	43 ± 19†	50 ± 10†	60 ± 14*,†	83 ± 20†
Base 2	38 ± 17	48 ± 11	51 ± 12*	79 ± 20
Post-VE	46 ± 19‡	50 ± 10	63 ± 14*,‡	82 ± 20‡
HR (beats/min)				
Base 1	112 ± 11	101 ± 7	115 ± 15	102 ± 16
PLR	111 ± 12*	97 ± 9	111 ± 13†	101 ± 13
Base 2	114 ± 12*	101 ± 6	115 ± 15*	102 ± 15
Post-VE	109 ± 11*	98 ± 6	105 ± 14‡	101 ± 15
SAP (mmHg)				
Base 1	95 ± 10*	106 ± 9	119 ± 13	111 ± 13
PLR	108 ± 9†	113 ± 12	134 ± 23*,†	112 ± 13
Base 2	96 ± 9*	107 ± 9	120 ± 13	111 ± 11
Post-VE	114 ± 9‡	111 ± 11	136 ± 20*,‡	121 ± 10‡
MAP (mmHg)				
Base 1	69 ± 8*	76 ± 6	73 ± 10	76 ± 9
PLR	79 ± 10	81 ± 9	86 ± 12†	77 ± 8
Base 2	69 ± 8	76 ± 6	73 ± 11	76 ± 7
Post-VE	83 ± 11	80 ± 7	88 ± 11‡	84 ± 9‡
PP (mmHg)				
Base 1	39 ± 13	45 ± 10	68 ± 15*	54 ± 15
PLR	42 ± 12	48 ± 11	73 ± 23†	55 ± 16
Base 2	39 ± 11	45 ± 10	70 ± 14*	54 ± 15
Post-VE	47 ± 11‡	47 ± 11	74 ± 20*,‡	57 ± 14
CO (L/min)				
Base 1	4.1 ± 1.6	4.7 ± 0.8	5.9 ± 1.5*	7.9 ± 2.1
PLR	4.5 ± 1.8†	4.8 ± 0.8	6.6 ± 1.6*,†	8.3 ± 2.0†
Base 2	4.1 ± 1.6	4.8 ± 1.0	5.9 ± 1.5*	8.0 ± 2.1
Post-VE	4.8 ± 1.8‡	4.8 ± 0.9	6.6 ± 1.5*,‡	8.3 ± 2.0‡

Values were shown as mean ± SD. *P<0.05 versus nonresponders; †P<0.05 versus baseline 1; ‡P<0.05 versus baseline 2. GEF: Global ejection fraction; CO: Cardiac output; HR: Heart rate; SAP: Systolic arterial pressure; MAP: Mean arterial pressure; PP: Radial pulse pressure; SV: Stroke volume;

accurate bedside prediction of fluid responsiveness regardless of whether cardiac function of the patients is normal (GEF ≥20%) or lower (GEF <20%), but the threshold, sensitivity, and specificity were lower in the GEF <20% group. In addition, PLR-ΔHR could predict fluid responsiveness in the GEF ≥20% group but not in the GEF <20% group, while pressure index changes were poorly able to predict fluid responsiveness.

Hypovolemia is a very frequent clinical situation in the ICU and is primarily treated with VE. Unfortunately, only 40–70% of critically ill patients with acute circulatory failure display a significant increase in SV or CO in response to VE.[1] In patients with septic shock, fluid infusion is usually recommended[26] but may be harmful particularly in patients with acute respiratory distress syndrome.[27,28] PLR as a simple, economic, noninvasive, and reversible self-VE can help ICU staff avoid fluid infusion in patients who could be harmed by fluid overload.[29-31] Recently, Monnet *et al*.[32] performed a systematic review and meta-analysis including 21 studies and concluded that PLR very reliably

PLR: Passive leg raising; VE: Volume expansion; SD: Standard deviation.

predicted volume responsiveness. However, none of these studies evaluated the systolic cardiac function of patients, so it remained unknown whether systolic cardiac function could influence the diagnostic accuracy of PLR. Therefore, we designed this study to explore the accuracy of PLR for detecting fluid responsiveness in patients with low or normal cardiac function.

Echocardiography is the gold standard for left ventricular ejection fraction (LVEF) estimation. However, the measurement of LVEF in ICU patients is commonly performed through bedside transthoracic echocardiography (TTE), and the quality of TTE is influenced by many factors such as mechanical ventilation. Thus, by providing cardiac function indices, the PiCCO system could provide an interesting alternative to echocardiography in the assessment of LVEF. Four previous studies validated GEF as an indicator of LVEF in critically ill ICU patients. Combes *et al*.[20] demonstrated in thirty patients that GEF was correlated with LVEF assessed by transesophageal echocardiography (r = 0.82; P < 0.0001). A similar correlation was described in 2009 by Jabot *et al*.[21] from F/LVEF measurements (r = 0.67; P < 0.0001) involving 39 patients where LVEF was obtained by TTE. Meybohm *et al*.[33] and Perny *et al*.[34] also suggested that GEF was significantly correlated with LVEF. Trof *et al*.[23] studied the effect of systolic cardiac function on cardiac filling volumes versus pressures for predicting fluid responsiveness by dividing patients into a low-GEF group (<20%) and a near-normal-GEF group (≥20%). However, the authors studied the effect of systolic function on static hemodynamic indices but not on dynamic indices. In our study, we also divided patients into a low-GEF group (<20%) and a near-normal-GEF group (≥20%). In fact, the GEF value was 12 ± 2% in the GEF <20% group, which was significantly lower than that (26 ± 3%) in the GEF ≥20% group. The other indices of SV, CO, CFI, CPO, and dp/dt max were also significantly lower in the GEF <20% group, which demonstrated the

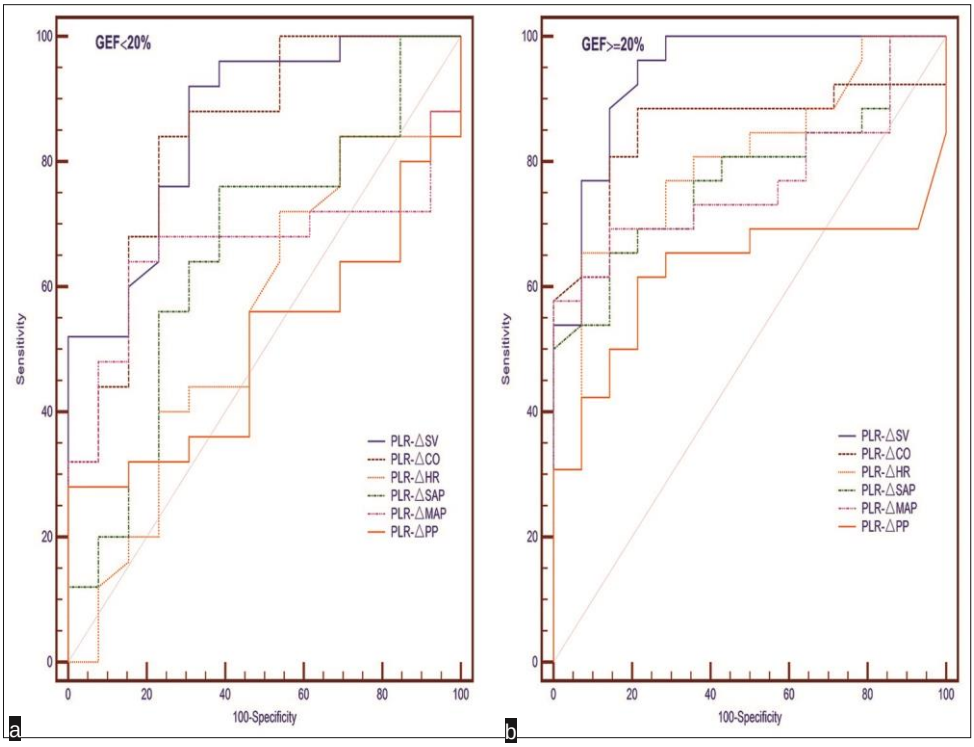

Figure 2: ROC curves comparing the ability of PLR-induced changes to discriminate responders from nonresponders regarding volume expansion in the GEF <20% group (a) and GEF ≥20% group (b). PLR: Passive leg raising; ROC: Receiver-operating characteristic; GEF: Global ejection fraction.

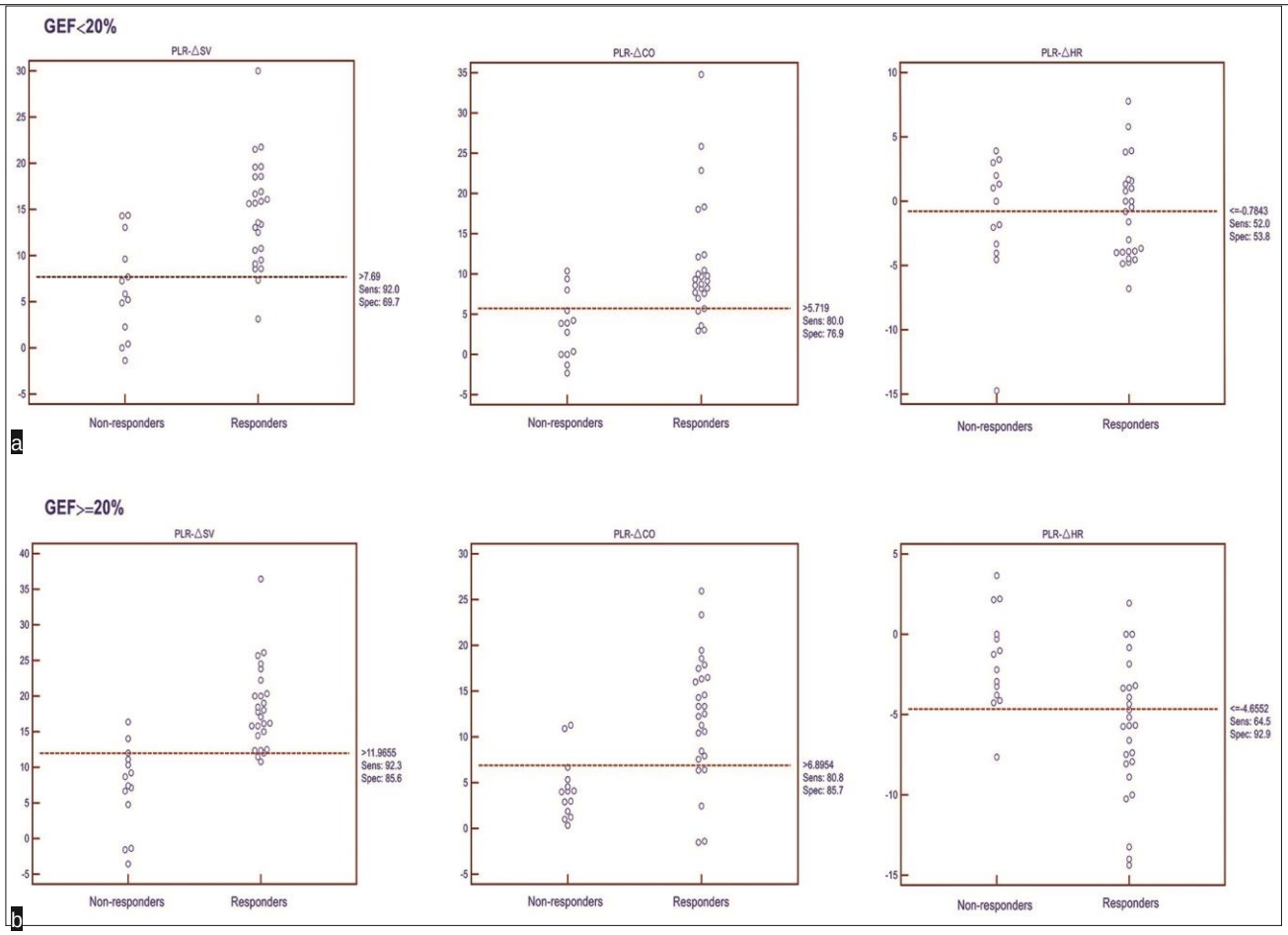

Figure 3: PLR-induced changes in stroke volume (ΔSV), cardiac output (ΔCO) and heart rate (ΔHR) in responders and nonresponders in the GEF <20% group (a, *n*=38) and the GEF ≥20% group (b, *n*=40). PLR: Passive leg raising; GEF: Global ejection fraction.

Table 3: Diagnostic accuracy of index changes induced by PLR for predicting fluid responsiveness

Items	GEF <20% (*n* = 38)								
	R	*P*	AUC	*P*	Threshold (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ΔSV	0.539	0.000	0.860 ± 0.059	0.000	8	92	70	85	82
ΔCO	0.494	0.002	0.840 ± 0.063	0.001	6	80	77	87	67
ΔHR	−0.096	0.568	0.457 ± 0.100	0.667	−1	52	54	70	39
ΔSAP	0.217	0.192	0.628 ± 0.091	0.113	6	76	62	79	57
ΔMAP	0.273	0.098	0.662 ± 0.091	0.106	7	64	77	84	53
ΔPP	0.205	0.216	0.502 ± 0.100	0.998	6	56	54	70	39
Items	**GEF ≥20% (*n* = 40)**								
	R	*P*	AUC	*P*	Threshold (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ΔSV	0.698	0.000	0.942 ± 0.038	0.000	12	92	86	92	84
ΔCO	0.712	0.000	0.859 ± 0.063	0.000	7	81	86	91	71
ΔHR	−0.533	0.000	0.799 ± 0.071	0.002	−5	65	93	94	60
ΔSAP	0.196	0.225	0.776 ± 0.073	0.004	5	69	78	86	58
ΔMAP	0.249	0.121	0.769 ± 0.075	0.005	7	69	72	82	57

△PP	0.220	0.212	0.624 ± 0.090	0.202	5	62	79	84	52

GEF: Global ejection fraction; PLR: Passive leg raising; PLR-△SV: PLR-induced change in stroke volume; PLR-△CO: PLR-induced change in cardiac output; PLR-△HR: PLR-induced change in heart rate; PLR-△SAP: PLR-induced change in systolic arterial pressure; PLR-△MAP: PLR-induced change in mean arterial pressure; PLR-△PP: PLR-induced change in pulse pressure; PPV: Positive predictive value; NPV: Negative predictive value; *r*: Correlation coefficient between PLR-△ and VE-△SV; AUC: Area under the receiver operation characteristics curve.

significant difference in systolic cardiac function between the two groups.

In our study, the threshold value and diagnostic accuracy of PLR to predict fluid responsiveness were dependent on systolic cardiac function. Both PLR-ΔSV and PLR-ΔCO enabled accurate bedside prediction of fluid responsiveness regardless of cardiac function, but the threshold, sensitivity, specificity, and AUC were all higher in the near-normal-GEF group (≥20%) than in the low-GEF group (<20%). According to the Frank–Starling curve, two zones can be distinguished: (a) a slope where minimum preload changes give rise to a marked increase in SV (preload dependency zone) and (b) a flat or level segment where the SV hardly varies with changes in preload (preload-independent zone). Therefore, the relationship between the changes in SV depends on the baseline of preload and morphology or the gradient of the curve, which are determined by the contractile capacity of the heart. Thus, different patients show different Frank–Starling curves because of varied cardiac function, indicating different responses to the same preload increase. In our study, the baseline GEDV was 737 ± 190 ml in GEF <20% group versus 695 ± 103 ml in GEF ≥20% group which means that there were no significant differences between the two groups (P = 0.369) in terms of baseline of preload. The patients were divided into a near-normal-GEF group and a low-GEF group, showing different Frank–Starling curves between the two groups. Our results also demonstrated that the threshold in the near-normal-GEF group was higher (ΔSV: 12% vs. 8%; ΔCO: 7% vs. 6%) than that in the low-GEF group. Interestingly, the threshold values of PLR-ΔCO were less than those of PLR-ΔSV regardless of cardiac function, which brought our attention to PLR-ΔHR. We found that PLR-ΔHR in the near-normal-GEF group and the low-GEF group were different. The decrease in HR (−6.0 ± 4.2%; P = 0.002) was statistically significant in responders but not in nonresponders of the GEF ≥20% group, and HR was not found to be altered in responders or nonresponders of the GEF <20% group. In addition, in the GEF ≥20% group, PLR-ΔHR was negatively correlated with VE-ΔSV (r = −0.533, P = 0.000). The threshold value of PLR-ΔHR for predicting fluid responsiveness was −5% using ROC analysis with acceptable sensitivity (65%) and high specificity (93%). However, in the GEF <20% group, PLR-ΔHR could not predict fluid responsiveness. This finding may be because (a) the parasympathetic component of baroreceptor regulation of HR was impaired in patients with cardiac dysfunction[35] or (b) the overstimulation of sympathetic nerves was inconsistent with the inhibition of the vagal nerve in patients with left ventricle dysfunction, which leads to uncoordinated control of autonomic nervous system and sinoatrial node, resulting in a disorder of HR regulation.[36] Préau *et al*.[17] also concluded that PLR-ΔHR was statistically significant (−2.0 ± 4.0%; P < 0.05) in responders, but they included few patients with low LVEF and did not distinguish between groups of patients. These authors stated that the observed decrease in HR was very small and thus had no impact. The use of pressure index changes, such as PLR-ΔPP, ΔSAP, and ΔMAP, as preload responsiveness markers is based on the hypothesis that they depend on SV. During each systole, the left ventricle ejects a variable amount of blood through the systemic arterial circulation generating PP, SAP, and MAP waves along the arterial tree. However, all these pressure indices are influenced by complex properties of the systemic arterial tree, such as arterial compliance, wave propagation, and wave reflection. Monnet *et al*.[32] concluded that, when PLR effects are assessed by changes in PP, the specificity of the PLR test remains acceptable but its sensitivity is poor; Préau *et al*.[17] also found that the accuracy of ΔSAP and ΔMAP for predicting fluid responsiveness is lower. In our study, all these pressure indices were poorly able to predict fluid responsiveness, which is consistent with previous studies.

Our study has some limitations. First, we used GEF <20% monitored by PiCCO to distinguish patients with cardiac dysfunction. The accuracy of GEF is lower than LVEF measurements by TTE or TEE, especially in patients with valvular regurgitation. However, previous studies have demonstrated a significant correlation between GEF and LVEF. Second, we defined fluid responsiveness as an increase in SV ≥15% with VE; this cutoff value was chosen in reference to previous studies.[32] Although this cutoff seems clinically relevant, the predictive value of PLR may be altered if another cutoff value were chosen. In addition, the VE for definition of fluid responsiveness might be influenced by cardiac function. For patients with cardiac dysfunction, the influence would never be eliminated only if the VE was performed when the cardiac function has been improved to the normal level. However, it is very difficult to titrate cardiac function with inotropic agents. Third, nearly one-third of patients were not given analgesic and sedative drugs during PLR, which may cause vital signs to fluctuate due to sympathetic arousal. However, PLR is a less sympathetic stimulation for these

patients who were more compatible and tolerated endotracheal intubation. In addition, there was no statistically significant difference in the proportion of patients without analgesic and sedative drugs between the two groups, which further reduced the possibility of experimental and result errors caused by sympathetic arousal. Finally, the study population was small but similar to previous PLR studies, so a large-scale study must be conducted to confirm these findings.

In conclusion, our study demonstrated that the diagnostic value of PLR depends on cardiac systolic function in ventilated patients in the ICU. PLR-ΔSV and PLR-ΔCO enabled accurate bedside prediction of volume responsiveness regardless of whether cardiac function of the patients is normal or lower, but the threshold, sensitivity, and specificity were lower in the GEF <20% group. In addition, PLR-ΔHR could predict fluid responsiveness in the GEF ≥20% group but not in the GEF <20% group, while pressure index changes were poorly able to predict fluid responsiveness. These findings suggest that, when using PLR for predicting fluid responsiveness, cardiac systolic function must be considered a factor influencing the diagnostic accuracy of PLR.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Hemodynamic changes induced by PLR and VE in responders and nonresponders in each group

Items	GEF <20% (*n* = 38)				GEF ≥20% (*n* = 40)			
	Responders (*n* = 25)	Nonresponders (*n* = 13)	*t*	*P*	Responders (*n* = 26)	Nonresponders (*n* = 14)	*t*	*P*
PLR-△SV	14.7 ± 5.7%	6.4 ± 5.3%	4.304	0.000	18.2 ± 5.8%	7.2 ± 5.9%	5.651	0.000
PLR-△CO	11.2 ± 7.5%	3.4 ± 2.3%	3.454	0.001	12.3 ± 6.7%	3.9 ± 3.4%	4.359	0.000
PLR-△HR	−0.9 ± 3.7%	−1.2 ± 4.9%	0.219	0.828	−6.0 ± 4.2%	−1.6 ± 3.0%	−3.341	0.002
PLR-△SAP	11.2 ± 7.8%	7.9 ± 6.5%	1.308	0.199	11.6 ± 8.8%	5.0 ± 2.7%	2.737	0.009
PLR-△MAP	10.5 ± 7.7%	6.3 ± 2.9%	1.848	0.073	13.9 ± 11.3%	5.2 ± 3.1%	2.801	0.008
PLR-△PP	10.4 ± 8.1%	5.9 ± 4.8%	0.744	0.454	8.0 ± 6.8%	4.3 ± 3.4%	0.863	0.073
VE-△SV	20.8 ± 5.5%	5.0 ± 3.7%	8.347	0.000	22.5 ± 5.4%	4.8 ± 4.1%	11.558	0.000

GEF: Global ejection fraction; PLR: Passive leg raising; PLR-△SV: PLR-induced change in stroke volume; PLR-△CO: PLR-induced change in cardiac output; PLR-△HR: PLR-induced change in heart rate; PLR-△SAP: PLR-induced change in systolic arterial pressure; PLR-△MAP: PLR-induced change in mean arterial pressure; PLR-△PP: PLR-induced change in pulse pressure; VE: Volume expansion; VE-△SV: VE-induced change in stroke volume.

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ORIGINAL

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Abstract Purpose: To assess sublingual microcirculatory changes following passive leg raising (PLR) and volume expansion (VE) in septic patients. Methods: This prospective study was conducted in two university hospital intensive care units and included 25 mechanically ventilated patients with severe sepsis or septic shock who were eligible for VE in the first 24 h of their admission. Pulse pressure variation (DPP), cardiac output (CO) and sublingual microcirculation indices were assessed at five consecutive steps: (1) semirecumbent position (Baseline 1), (2) during PLR manoeuvre (PLR), (3) after returning to semi-recumbent position (Baseline 2), (4) at the time when VE induced the same degree of preload responsiveness VE (VE_{END}). At each step, five sublingual microcirculation sequences were acquired using sidestream darkfield imaging to assess functional capillary density (FCD), microcirculatory flow index (MFI), proportion of perfused vessels (PPV) and flow heterogeneity index (FHI).

Results: The PLR, $VE_{DPP = PLR}$ and VE_{END} induced a significant increase in CO and a significant decrease in DPP compared to Baseline 1 and Baseline 2 values. Both PLR and VE induced significant increases in FCD, MFI and PPV and a significant decrease in FHI compared to Baseline 1 and Baseline 2 values.

Conclusions: In preload responsive severe septic patients examined within the first 24 h of their admission, both PLR and VE improved sublingual microcirculatory perfusion. At the level of volume infusion used in this study, these changes in sublingual microcirculation were not explained by changes in rheologic factors or changes in arterial pressure.

Keywords Microcirculation Sepsis Shock Volume expansion

as PLR ($VE_{DPP = PLR}$) and (5) at the end of	Fluid responsiveness	Passive leg raising	Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and

septic shock patients

Introduction

Altered microcirculatory blood flow is a major pathophysiological feature of severe sepsis and septic shock [1]. De Backer et al. [2] showed that microvascular density and microvascular blood flow are both reduced in septic patients compared to healthy volunteers or nonseptic intensive care unit (ICU) patients. Moreover, the degree of microvascular impairment has a prognostic value since it worsens in non-surviving septic patients compared to those who ultimately overcome their septic episode [3]. Early systemic haemodynamic resuscitation of septic patients may improve the time-course of microcirculatory dysfunction and eventually the patient's outcome [4, 5]. However, relationships between systemic haemodynamic and microcirculatory changes during resuscitation are complex. In this regard, dobutamine infusion did not induce parallel changes in systemic and sublingual blood flows in septic shock patients [6].

Fluid resuscitation is one of the major therapies aimed at restoring blood pressure and cardiac output (CO) in severe septic patients in the early period as well as in the later phase [7, 8].

Fluid loading may improve microcirculatory blood flow through either systemic effects (such as increased perfusion pressure and/or increased CO), rheologic changes [9] (decreased microvascular blood viscosity) or local vasodilation (shear stress).

The aim of the study reported here was to assess sublingual microcirculatory changes in response to volume expansion (VE) in severe sepsis and septic shock patients eligible for VE within the first 24 h of their admission in the ICU. In order to distinguish between the haemodynamic and rheologic effects of VE on sublingual microvessel perfusion, we also performed passive leg raising (PLR), which is a manoeuvre that mimics VE in terms of preload-related haemodynamic consequences [10, 11] but which is assumed not to exert any rheologic effect. This work has previously been presented in abstract form [12].

Materials and methods

Patients

This observational study was approved by our local Institutional Review Board (Comite´ Consultatif de Protection des Personnes dans la Recherche Biome´dicale de Bice^tre), which waived the need for written informed consent. It was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki. Patients were recruited in the surgical and medical ICUs of Bice^tre University Hospital between July

2007 and January 2008. Inclusion criteria were (1) state of severe sepsis or septic shock, as defined by the 2001 SCCM/ ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [13], within the first 24 h of admission to the ICU, (2) preload-dependency, defined by respiratory variations in arterial pulse pressure (DPP) greater than 13% [14] and (3) eligibility for VE according to our local guidelines: mean arterial pressure (MAP)\65 mmHg (or a decrease [30 mmHg in previously hypertensive patients), urine output\0.5 mL/kg/h for 2 h and presence of skin mottling. Exclusion criteria were pregnancy, age \18 years, contraindication either to PLR (unstable spine fracture, orthopaedic transtibial leg traction, increased intracranial pressure) or to VE (suspected or confirmed hydrostatic pulmonary oedema), non-sinus rhythm and spontaneous breathing or ventilator triggering. Patients were sedated (midazolam/sufentanil) and mechanically ventilated in volume-controlled mode with a tidal volume C7 mL/kg and a 1:2 inspiratory to expiratory ratio.

We recorded the Simplified Acute Physiology Score (SAPS II) [15], the Acute Physiology and Chronic Health Evaluation (APACHE II) score [16] on admission and the Sepsis-related Organ Failure Assessment (SOFA) score [17] at inclusion.

Haemodynamic measurements

The DPP was calculated as previously described [14]. As part of routine CO monitoring, patients had either a continuous pulse contour analysis device or an oesophageal Doppler monitor. Details concerning haemodynamic data acquisition are provided in the Electronic Supplementary Material (ESM). At each step of the study, a full set of haemodynamic data was obtained, including heart rate (HR), systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures, CO, stroke volume (SV) and DPP.

Microcirculatory measurements and analysis

Sublingual microcirculation videos were obtained using a side-stream dark field imaging device (SDF; Microscan, MicroVisionMedical, Amsterdam, the Netherlands) derived from the orthogonal polarized spectral imaging technology [18]. Images acquisition and analysis were performed following international recommendations [19] with dedicated software analysis [Automated Vascular Analysis (AVA) ver. 1.0; Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands] as described in the ESM. All sequences were acquired by the same investigator (JP) and then randomly allocated to an alphanumeric code so that neither the patient's name nor the study step could be identified by a second investigator (SD) that performed the analysis.

Raw quantitative variable assessed with AVA software was functional capillary density (FCD, lm^{-1} or cm cm^{-2}). As small vessels usually account for more than 90% of sublingual microvasculature and are the most altered in sepsis [2], subsequent analyses were restricted to the small vessel category. Semi-quantitative analysis with AVA provided the microcirculatory flow index (MFI), the proportion of perfused vessels (PPV, %) and the flow heterogeneity index.

Study design

Haemodynamic and microcirculatory indices were assessed at five consecutive steps: (1) semi-recumbent position (Baseline 1), (2) during PLR manoeuvre (PLR), (3) after returning to semi-recumbent position (Baseline 2), (4) at the time when VE induced the same degree of preload responsiveness as PLR ($VE_{DPP = PLR}$) and (5) at the end of VE (VE_{END}) (see ESM and ESM Fig. 1 for details). Volume expansion was performed over 30 min using a maximal volume of either 500 mL normal saline or 500 mL hydroxyethyl starch solution 6% (HES 130/ 0.4; Voluven, Fresenius Kabi, Se`vres, France) according to the attending physician's decision. Haemoglobin concentration was measured at the beginning of the study and immediately after VE_{END}. The ventilator settings, sedative and vasoactive drugs infusion rates were kept constant throughout the study. Patients were followed up for 28-day in-hospital mortality and duration of hospital stay.

Statistical analysis

The distribution of all datasets was checked for normality using the Shapiro–Wilk test and normal chi-square goodness of fit. In the case of non-Gaussian distribution, data were expressed as the median (25th–75th percentiles) and analysed with non-parametric tests: Mann–Whitney test, Spearman correlation q, Wilcoxon matched pairs test and Friedman test followed by the Wilcoxon test with Bonferroni correction. When data followed a normal distribution, the results were expressed as mean ± standard deviation (SD) and analysed using paired Student t test and repeated-measures analysis of variance (ANOVA). We checked that there was no association between the type of solution and the changes in the microcirculatory indices. A P value\0.05 was considered to be statistically significant. Data were analysed using StatEl (adScience, Paris, France; http:\\www.adscience.eu) and Prism4 (GraphPad, San Diego, CA) software. A sample size of n = 25 patients was chosen on the basis of feasibility and because for any variable of interest, this sample size allowed a 80% power to detect an effect size (i.e. mean change/standard deviation of change) around

0.65, that was considered as physiologically meaningful, with a alpha risk at 5% adjusted form multiplicity.

Results

Patient characteristics

Twenty-five septic patients (20 with septic shock and 5 with severe sepsis) were included in this study over a 6-month period. Table 1 shows the patient characteristics.

Systemic haemodynamic effects of PLR and VE. No adverse event occurred during the study period. The CO was assessed using a continuous pulse contour analysis device and an oesophageal Doppler monitor in 13 and 12 patients, respectively. The VE was performed with normal saline in eight patients and 6% hydroxyethyl starch solution in 17 patients. The time course of HR, MAP, CO, SV and DPP throughout the five sequential study steps is presented in Table 2. The HR remained unchanged throughout the protocol. Compared to Baseline 1, PLR simultaneously induced a significant increase in CO and SV and a significant decrease in DPP. No significant

Table 1 Baseline characteristics of study subjects (n = 25)

Age (years)	57 ± 17
Sex (M/F)	16/9
Weight (kg)	79 ± 19
SAPS II score (admission)	45 (37–56)
APACHE II score (admission)	22 (19–27)
SOFA score (inclusion)	12 (9–13)
Time from ICU admission to inclusion (days)	1 (0–1)
Time from sepsis onset to inclusion (days)	1 (1–2)
ICU length of stay (days)	20 (9–24)
In-hospital outcome (S/D)	17/8
Reason for inclusion	
Septic shock	20
Severe sepsis	5
Primary site of infection	
Abdomen	12
Lung	5
Soft tissue	5
Urinary tract	3
Catecholamine, n; dose (lg kg^{-1} min^{-1})	
None	5
Norepinephrine	17; 0.40 (0.24–0.78)
Epinephrine	3; 0.39 (0.20–0.42)
Body temperature (C)	37.5 (36.7–38)

Ramsay score	5 (5–6)
Tidal volume (mL kg^{-1})	8 (7.3–8.4)
Plateau airway pressure (cmH_20)	20 (18–25)
PEEP (cmH_2O)	5 (4–6)

Values are given as the mean ± standard deviation (SD) or median (25th–75th percentiles) according to data distribution

M Male, F female, SAPS Simplified Acute Physiology score, APACHE Acute Physiology and Chronic Health Evaluation score, SOFA Sepsis-related Organ Failure Assessment score, ICU intensive care unit, S survivor, D dead, PEEP positive end expiratory pressure

Table 2 Time-course of systemic haemodynamic indices throughout the protocol (n = 25)

Parameters	Baseline 1	PLR	Baseline 2	$VE_{DPP = PLR}$	VE_{END}	P ANOV
HR (min^{-1})	100 ± 17	98 ± 18	98 ± 18	97 ± 18	96 ± 19	NS
MAP (mmHg)	72 ± 15	73 ± 16	73 ± 14	80 ± 15*§	81 ± 17*§	\0.001
CO (L min^{-1})	5.1 ± 1.5	6.0 ± 1.7*	5.1 ± 1.5	5.9 ± 1.5*	6.5 ± 1.6*§	\0.001
SV (mL)	52 ± 16	62 ± 20*	54 ± 19	62 ± 18*	69 ± 20*§	\0.001
DPP (%)	22 ± 5	15 ± 5*	21 ± 5	15 ± 5*	12 ± 7*§	\0.001

Values are given as the mean ± SD. Only those parameters who were significant are given

PLR passive leg raising, VE volume expansion, NS non-significant, HR heart rate, MAP mean arterial pressure, CO cardiac output, SV stroke volume, DPP respiratory variation in arterial pulse pressure, ANOVA analysis of variance

* P\0.001 versus Baseline 1 and Baseline 2

§ P\0.001 versus PLR

P\0.001 versus $VE_{DPP = PLR}$

difference in any of the haemodynamic indices was found between Baseline 1 and Baseline 2. At the first step of VE ($VE_{DPP = PLR}$), MAP, CO and SV were significantly increased compared to both Baseline 1 and Baseline 2 values, and these increases (except for MAP) were not significantly different compared to those at the PLR step. At the end of VE (VE_{END}), CO and SV increased yet further, and DPP continued to decrease. Neither baseline haemodynamics nor VE-induced changes in haemodynamic indices were statistically different between the two subgroups of patients who received either normal saline or hydroxyethyl starch solution, respectively.

Microcirculatory effects of PLR and VE. We performed 125 SDF studies and therefore recorded 625 video sequences in the 25 septic patients. At Baseline 1, the distribution of microvessels in relation to their diameter was as follows: small vessels, 96.3%; medium vessels, 3.6%; large vessels, 0.03% (data not shown). This distribution was unaltered during the experimental protocol. The time-courses of FCD, MFI, PPV and the flow heterogeneity index during the study period are depicted in Fig. 1a–d, respectively. No significant difference was seen between Baseline 1 and Baseline 2 in terms of the following microvascular indices: FCD, MFI, PPV, and the flow heterogeneity index. The PLR, $VE_{DPP = PLR}$ and VE_{END} significantly increased FCD, MFI and PPV compared to the values at Baseline 1 and Baseline 2. The heterogeneity index was significantly reduced by both PLR and VE. Baseline 1 and Baseline 2 values of FCD, MFI, PPV and the heterogeneity index were not significantly different between the patients who received normal saline and those who received hydroxyethyl starch solution. VE-induced changes in microcirculatory indices were also not significantly different between patients receiving normal saline and those receiving the hydroxyethyl starch solution. Haemoglobin values at the beginning of the protocol (Baseline 1: 9.8 ± 1.6 g/dL) and immediately after VE (VE_{END}: 9.5 ± 1.5 g/dL) were not significantly different for the whole population. However, hydroxyethyl starch-induced VE was associated with a statistically significant decrease in haemoglobin from Baseline 1 (10.3 ± 1.3 g/dL) to VE_{END} (9.8 ± 1.4, P = 0.007) that was not evidenced in saline-infused patients (P = 0.49). At either baseline or after VE (data not shown), the microcirulatory scores of septic shock patients (n = 20) who received norepinephrine or epinephrine were not significantly different from those of severe sepsis patients (n = 5) without vasoactive drugs. Examples of sublingual microcirculation videos in the same patient at the five steps of the protocol can be seen in the ESM (Animations 1, 2, 3, 4 and 5).

Relationship between microcirculatory perfusion and systemic haemodynamics

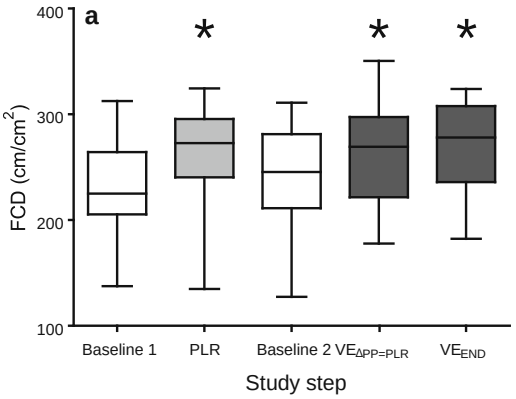
There was no statistically significant relationship between PLR-induced changes in macrocirculatory and microcirculatory indices.

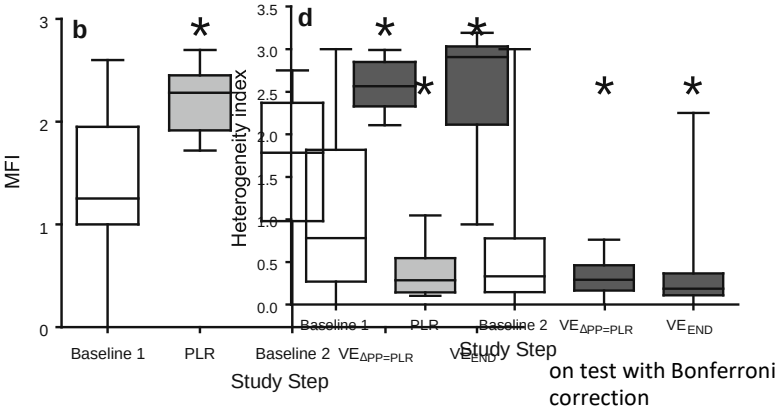
At VE_{END}, VE-induced changes in MFI positively and significantly correlated with VE-induced changes in CO (q= 0.53, P\0.006; ESM Fig. 2a) and MAP (q= 0.47, P\0.018; ESM Fig. 3a). Changes in PPV induced by VE also correlated with VE-induced changes in CO (q= 0.51, P\0.005; ESM Fig. 2b) but not with VE-induced changes in MAP (q= 0.29, P = NS; ESM Fig. 3b). No other significant correlation was found between VE-induced changes in microcirculatory indices and macrocirculatory indices.

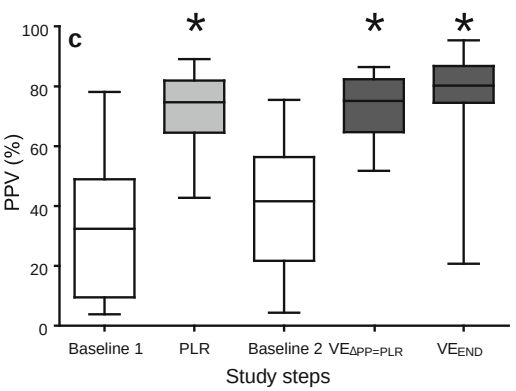
Discussion

Our study shows that both PLR and VE induced a significant sublingual microcirculatory improvement in preload-dependent patients with severe sepsis

and septic shock. Indeed, both PLR and VE simultaneously increased vessel density (increased FCD) and vessel perfusion (increased MFI and PPV) and reduced microvascular heterogeneity. Among the microcirculatory variables







b Fig. 1 Time-course of sublingual functional capillary density (FCD, cm cm^{-2}) (a), microcirculatory flow index (MFI) (b), proportion of perfused vessels (PPV, %) (c) and flow heterogeneity index (d) throughout the protocol. Baseline 1 patient lying in the 45 semi-recumbent position. PLR Passive leg raising: simultaneous elevation of the lower limbs and lowering of the patient's trunk to the supine position using automatic bed elevation technique. The hip angle remains constant. PLR induces a reduction in DPP (respiratory variations in arterial pulse pressure). Baseline 2 same as Baseline 1. $VE_{DPP = PLR}$, the study step obtained when the volume expansion-induced decrease in DPP reaches the PLRinduced DPP value. VE_{END} End of volume expansion. The median is shown by the horizontal line within the box. The values between the lower and upper quartiles (25th–75th centiles) are within the box. Whiskers Minimum and maximum values. *P\0.05 vs. Baseline 1 and Baseline 2; Friedman test followed by the Wilcox on test with Bonferroni correction

investigated, MFI is known to be rather sensitive to flow variations, while FCD and PPV are more directed towards recruitment of the microcirculation. This opposite relationship between changes in MFI or PPV and changes in heterogeneity is in accordance with the results of an experimental study [20] in which animals were bled, thus producing effects in the opposite direction in comparison with those of our study. To the best of our knowledge, these results have not yet been reported in the clinical setting. It has been shown that the application of early goal-directed therapy in septic patients [7] may induce early improvement in sublingual microvascular flow [4] in association with reduced multi-organ failure [5]. Unlike the aforementioned studies, in which microvascular improvement was the result of a global therapeutic approach (including fluid loading, vasopressors, inotropes and blood products), in targeting systemic haemodynamic endpoints, we obtained haemodynamic assessment and SDF images at predefined steps during calibrated manoeuvres of increased preload. The results observed at the different steps of our protocol may enable clinicians to obtain a better understanding of the links between microcirculation and macrocirculation. Indeed, among our patient cohort, microvascular perfusion improvement with VE was not associated with changes in rheologic factors or changes in MAP.

Potential mechanisms of sublingual microcirculatory improvement

The PLR is assumed not to exert any rheologic effect since blood content remains unaltered. A recent study in patients with shock showed that the haemodynamic effects of PLR are only related to increased cardiac preload [21]. Interestingly, in our study, a similar improvement in microcirculatory perfusion was observed after PLR or VE. It is thus unlikely that the changes in

microcirculatory perfusion induced by the VE were due to changes in rheologic factors. Based on the results of an experimental study involving severe sepsis patients, Castro et al. [22] reported increases in blood viscosity, decreases in erythrocyte deformability and increases in erythrocyte aggregation in patients receiving hydroxyethyl starch in comparison with those receiving saline. By contrast, we did not observe significant differences in microcirculatory perfusion between patients infused with normal saline and hydroxyethyl starch solution. However, it should be stressed that these conclusions should be limited to the range of changes in rheologic factors associated with the amount of fluid we administered (i.e. 500 mL). In our study, VE-induced changes in MFI were positively correlated with VE-induced changes in MAP (q= 0.47) and CO (q= 0.53), and VE-induced changes in PPV correlated with VE-induced changes in CO (q= 0.51). These results are in agreement with those reported by Trzeciak et al. [4] showing correlations between macrocirculatory and microcirculatory variables in patients studied within 6 h of early goal-directed therapy. However, in our study, MAP did not appear to have a major effect on microcirculation. Indeed, microcirculatory changes were similar during PLR, which was associated with unchanged MAP, and after VE, which was associated with increased MAP up to 7 mmHg on average. Lafanechere et al. [23] also reported such different changes in MAP during PLR and VE in preloadresponsive patients. Whether the unchanged MAP during PLR is related to changes in vasomotor tone cannot be excluded, although the hypothesis of altered adrenergic tone during PLR has been refuted by previous investigators [21]. Changes in microcirculatory perfusion were associated with increases in CO induced either by PLR or VE. However, this relationship was not linear since the microcirculatory perfusion remained stable despite the additional increase in CO induced by the second step of the VE (VE_{END}), suggesting that a threshold was reached. In addition, it should be stressed that the magnitude of the changes in microvascular variables (?94% for MFI, ?205% for PPV) was disproportionate compared to that of the changes in CO (?27%). These two points suggest that different mechanisms are implicated in the regulation of microvascular perfusion and in the changes in CO, respectively. Elucidation of the nature of the relation between changes in CO induced by PLR or VE and changes in microcirculatory variables was beyond the scope of our investigation. We may postulate that the increase in CO with PLR and VE further increased microcirculatory perfusion through shear stress-related vasodilation. Neuro-mediated mechanisms interfering with microvascular flow regulation can also be involved. We cannot exclude that changes in sublingual perfusion during PLR were related, at least in part, to putative changes in vasomotor tone. However, and as reported by others [21, 24], the unchanged HR throughout our study makes unlikely the possibility of altered sympathetic tone that could have changed the distribution of blood flow within the macro- or microcirculation.

These data support the hypothesis that VE can improve microcirculatory perfusion during the early period of resuscitation in severe sepsis and septic shock patients. At this stage, this microcirculatory improvement is accompanied by systemic haemodynamic changes, although no causal relationship has yet been established between the regulation of microvascular perfusion and changes in CO, suggesting that different mechanisms are involved.

Limitations of the study

Microvascular analysis was conducted in a blinded fashion and performed with the greatest care in order to avoid pressure artefacts; the most recent published recommendations for such studies were followed [19]. However, the following aspects must be acknowledged: (1) the sidestream dark field

imaging device only provides a twodimensional estimate of a three-dimensional network; (2) the suction device used induced negative pressure, which may have changed the microcirculatory blood flow by interfering with driving pressure. A question which remains to be answered is whether the sublingual mucosa is representative of other areas. A recent experimental study performed by Verdant et al. [25] in pigs with cholangitis support the hypothesis that the sublingual region can indeed be used to monitor the microcirculation in sepsis.

Due to its observational design, our study suffers from a non-standardized VE regimen and a non-standardized measure of CO since both were left to the discretion of the attending physician. However, both the pulse contour analysis device and oesophageal Doppler monitor provide real time CO monitoring and are able to estimate rapid changes in SV [26]. By recruiting only preload-responsive patients, our study design may have favoured some correlation between CO and microcirculatory variables since patients were expected to increase CO after VE. It would have been interesting to also have included patients not predicted to be fluid responders in order to evaluate what would have been their microvascular response. This point should be addressed in future studies. As some of the changes in CO were very large, we cannot exclude the possibility that spontaneous changes in the underlying condition also occurred in those early septic shock patients during the data acquisition period. However, a randomized trial including a group without VE would have been unethical. Another limitation is that we investigated patients at an early period of their disease. Therefore, our results cannot be extrapolated to septic patients receiving VE after the first 24 h of their admission in the ICU.

Conclusions

In preload-responsive patients with severe sepsis and septic shock patients studied during the first 24 h of their ICU stay, both PLR and VE improved sublingual microcirculatory perfusion obtained using side-stream dark field imaging. At the level of VE used in our study, changes in microcirculation were not explained by changes in rheologic factors or changes in MAP. We observed a non-linear relationship between changes in CO and changes in a number of microvascular variables. In addition, the observed changes in microvascular variables were disproportionate compared to changes in CO. These two points suggest that different mechanisms are implicated in the regulation of microvascular perfusion and in the changes in CO.

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Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis*

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Objective: **Rapid fluid loading is standard treatment for hypovolemia. Because volume expansion does not always improve hemodynamic status, predictive parameters of fluid responsiveness are needed. Passive leg raising is a reversible maneuver that mimics rapid volume expansion. Passive leg raising-induced changes in stroke volume and its surrogates are reliable predictive indices of volume expansion responsiveness for mechanically ventilated patients. We hypothesized that the hemodynamic response to passive leg raising indicates fluid responsiveness in nonintubated patients without mechanical ventilation.**

Design: **Prospective study.**

Setting: **Intensive care unit of a general hospital.**

Patients: **We investigated consecutive nonintubated patients, without mechanical ventilation, considered for volume expansion.**

Interventions: **We assessed hemodynamic status at baseline, after passive leg raising, and after volume expansion (500 mL 6% hydroxyethyl starch infusion over 30 mins).**

Measurements and Main Results: **We measured stroke volume using transthoracic echocardiography, radial pulse pressure usume, pulse pressure, and ing an arterial catheter, and peak velocity of femoral artery flowpancreatitis. using continuous Doppler. We calculated changes in stroke vol-velocity of femoral artery flow induced by passive leg raising (respectively, stroke volume, pulse pressure, and velocity of femoral artery flow). Among 34 patients included in this study, 14 had a stroke volume increase of >15% after volume expansion (responders). All patients included in the study had severe sepsis (n 28; 82%) or acute pancreatitis (n 6; 18%). The stroke volume >10% predicted fluid responsiveness with sensitivity of 86% and specificity of 90%. The pulse pressure >9% predicted fluid responsiveness with sensitivity of 79% and specificity of 85%. The velocity of femoral artery flow >8% predicted fluid responsiveness with sensitivity of 86% and specificity of 80%.**

Conclusions: **Changes in stroke volume, radial pulse pressure, and peak velocity of femoral artery flow induced by passive leg raising are accurate and interchangeable indices for predicting fluid responsiveness in nonintubated patients with severe sepsis or acute pancreatitis.(Crit Care Med 2010; 38:819–825)**

KEY WORDS: fluid responsiveness; leg raising; stroke volume; pulse pressure; blood flow; Doppler; echocardiography; sepsis;

Blood volume is a determinant of hemodynamic stability, which determines oxygen supplied to the tissues. Rapid infusion of crystalloids or colloids is the usual treatment for symptomatic hypovolemia. Because blood volume cannot easily be measured at the bedside, physicians need to know whether left ventricular stroke volume (SV) increases with volume expansion (VE) (1–3).

***See also p. 989.**

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Cardiac preload estimation is not an accurate method for predicting fluid responsiveness in patients with acute circulatory failure (1). Dynamic indices, based on analysis of SV preload dependence, have been validated to predict fluid responsiveness in mechanically ventilated patients (3). Such indices are also needed for spontaneously breathing patients. Passive leg raising (PLR) is a reversible maneuver that mimics rapid VE by shifting venous blood from the lower limbs (4) toward the intrathoracic compartment (5, 6). Thus, PLR increases the cardiac preload and, by definition, increases SV if the heart is preloaddependent (7–9).

Recent studies demonstrated that PLR-induced changes in SV (SV) and cardiac output are reliable predictive indices of VE responsiveness, whatever the breathing conditions (10–13). The SV, measured by transthoracic echocardiography (11, 12), is an accurate index of fluid responsiveness, but its feasibility is variable and depends on patient echogenicity, hospital equipment, and physicians' skills in echocardiography.

PLR-induced change in systemic arterial pulse pressure (PP) is another hemodynamic parameter that detects preload responsiveness (10, 14). Its measurement requires ordinary critical care equipment and expertise, but PP has been demonstrated to be less accurate than PLRinduced change in aortic blood flow at detecting VE responsiveness in mechanically ventilated patients (14, 15). To our knowledge, no study has compared the accuracy of PP with that of PLRinduced change in blood flow for predicting fluid-loading responsiveness in nonintubated patients.

Echo Doppler of peripheral arteries permits noninvasive measurement of changes in peripheral artery flow. Those measurements are independent of transthoracic echogenicity and the presence of

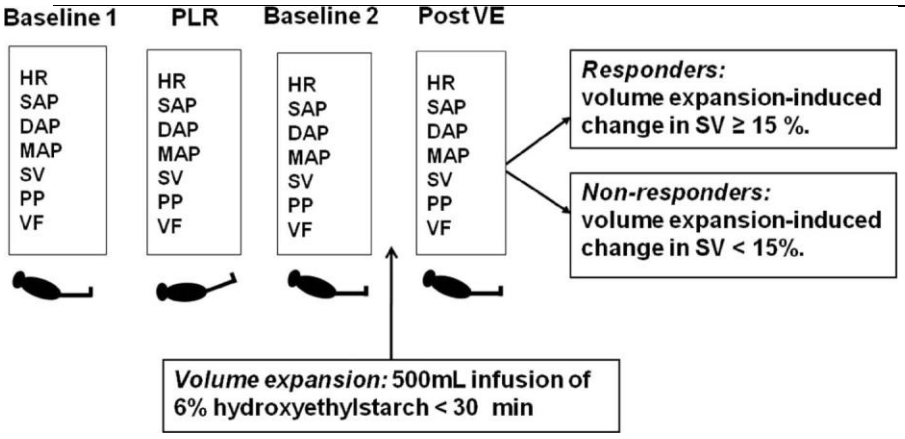


Figure 1. Study design. *PLR*, passive leg raising; *VE*, volume expansion; *HR*, heart rate; *SAP*, systolic arterial pressure; *DAP*, diastolic arterial pressure; *MAP*, mean arterial pressure; *PP*, radial pulse pressure; *SV*, stroke volume; *VF*, peak velocity of femoral artery flow; *SV*, *PP*, and *VF*, PLR-induced changes in SV, PP, and VF, respectively.

an arterial catheter. Thus, when SV and PP are not available, PLR-induced change in peripheral artery flow could be measured. To our knowledge, no study has tested PLR-induced change in peripheral artery flow measured by echo Doppler to predict preload responsiveness.

The SV as measured by transthoracic echocardiography, PP as measured by radial catheter, and PLR-induced change in the peak velocity of femoral artery flow (VF), as measured by echo Doppler, are three different methods for hemodynamic assessment. When one of these indices is not measurable, it can be replaced by another if accuracy for predicting fluid responsiveness is identical. However, their relative accuracy at predicting VE responsiveness is not clearly established.

The aim of this study was to test whether SV, PP, and VF are equally accurate at predicting VE responsiveness in nonintubated patients with acute circulatory failure, thus rendering them interchangeable.

MATERIALS AND METHODS

This study was submitted to the Institutional Review Board for human subjects of our institutions. The protocol was approved and was considered to be part of routine practice. Patients were informed before participation in the study.

Patients

Two echocardiographists (S.P. and F.D.) prospectively assessed consecutive patients hospitalized in the critical care unit (21 beds) of the general hospital center in Valenciennes

ical System; Bothell, WA) with a 2-MHz transthoracic transducer. Aortic blood flow was recorded with pulsed Doppler at the level of the aortic valve so that the click of the aortic closure was obtained. The velocity time integral of aortic blood flow was measured. The aortic valve area was calculated from the diameter of the aortic orifice, measured at the insertion of the aortic cusps, as aortic area $(\text{aortic diameter}/2)^2$. SV was calculated as SV aortic valve area the velocity time integral of aortic blood flow (16). Femoral blood flow was recorded with continuous Doppler at the level of the common femoral artery. One of the two common femoral arteries was identified with echographic twodimensional and color Doppler

modes. VF was measured with continuous Doppler.

Because hemodynamic values may vary within a respiratory cycle (17), an average of 10 consecutive cardiac cycles, over at least one respiratory cycle, was used for measurements of SAP, DAP, MAP, PP, SV, and VF. Measurements started at the lowest value of each index within a respiratory cycle.

Study Design

Figure 1 illustrates the design of the study. Hemodynamic measurements (heart rate, SAP, DAP, MAP, PP, VF, and SV) were recorded at each step of the protocol. Baseline 1 indicates that patients were in a semirecumbent position, with the trunk elevated 30° to 45° relative to the lower limbs, who were horizontal (baseline position). PLR indicates that patients were in a supine position with the lower limbs elevated 30° to 45° relative to the trunk, who was horizontal. Each hemodynamic measurement was recorded within the first 5 mins. Relative changes in hemodynamic indices induced by PLR are expressed in percentages as follows: change (%) 100 (PLR value baseline 1 value)/baseline 1 value. Baseline 2 indicates that the lower limbs and trunk were returned to baseline position for at least 5 mins. After hemodynamic measurements, VE was performed within 30 mins by infusing 500 mL of 6% hydroxyethyl starch (Voluven; Fresenius Kabi, Se`vres, France). Post-VE indicates that after VE, patients remained in the baseline position. Relative changes in hemodynamic indices induced by VE are expressed in percentages as follows: change (%) 100 (post-VE value baseline 2 value)/baseline 2 value. Patients were considered as responders to VE if their SV increased by 15%. Because the aortic valve area is not affected by VE, this 15% cut-off value was chosen before the beginning of the study as being twice the intraobserver variability of the velocity time integral of the aortic valve flow, measured by transthoracic echocardiography in previous studies (11, 12, 16, 17).

Table 1. Descriptive clinical data

	Responders, n 14	Nonresponders, n 20	*p*
Age, yrs	55 20	5219	.61
Sex ratio, M/F	6/8	13/7	.30
SAPS II	33.712.8	32.5 12.6	.78
In-hospital mortality	2 (14%)	2 (10%)	1
ICU stay before inclusion, days[a]	1 (0–5)	0 (0–3)	.31
OALL	0 (0%)	1 (5%)	1
COPD	0 (0%)	2 (10%)	.50
Arterial hypertension	8 (57%)	5 (25%)	.46
LVEF 45%	3 (21%)	2 (10%)	.63
Indication for ICU stay (on the day of inclusion) Sepsis	13 (93%)	15 (75%)	.36
Pulmonary infections	7 (50%)	10 (50%)	1
Urine tract infections	3 (21%)	2 (10%)	.63
Abdominal infections	2 (14%)	1 (5%)	.56
Other infections	1 (7%)	2 (10%)	1
Nosocomial infections	6 (43%)	5 (25%)	.46
Acute pancreatitis	1 (7%)	5 (25%)	.36
Clinical hemodynamic parameters Arterial hypotension	8 (57%)	10 (50%)	1
Oliguria	8 (57%)	11 (55%)	1
Tachycardia	10 (71%)	13 (65%)	1
Mottled skin	6 (43%)	3 (15%)	.12
Vasoactive drugs	2 (14%)	4 (20%)	1

SAPS II, Simplified Acute Physiologic Score II; ICU, intensive care unit, OALL, obliterating arteriopathy of the lower limbs; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

[a]Values expressed as median and interquartile range (25^{th}–75^{th} percentiles). Values are expressed as number (%) or mean SD.

Statistical Analysis

Numerical data are given as mean SD except when otherwise indicated. The Shapiro-Wilk test was used to test for normal distribution. All numerical variables were normally distributed in responders and nonresponders except for the "ICU stay before inclusion." Comparisons before and after PLR, before and after VE, and between baseline 1 and baseline 2 were performed using a pairedsample Student's *t* test. The comparison between responder and nonresponder values was performed using an independent-sample Student's *t* test except for the "ICU stay before inclusion," which was compared using the Mann-Whitney *U* test. Qualitative variables were reported as number and percentage and compared between groups using a Fisher test. Linear correlations were tested using the Pearson test and linear regression method. The receiver-operating characteristic curves SE were compared using the Hanley-McNeil test (18). Cut-off values for SV, PP, and VF were chosen to correspond to the best respective Youden's index (19) calculated as follows: Youden's index sensitivity specificity 1. Threshold indicator values such as sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for each hemodynamic indicator tested. A *p* .05 was considered statistically significant. Statistical analysis was

same observer (SP, intraobserver variability) and by a second observer (FD, interobserver variability). Intraobserver and interobserver variabilities for SV were, respectively, 3.7% 1.8% and 7.2% 4.7%. Intraobserver and interobserver variabilities for VF were, respectively, 2% 1.2% and 8.4% 9.2%.

The results were obtained with SAP, DAP, MAP, PP, SV, and VF measured over an average of 1.6 .2 respiratory cycles. For the group as a whole, SV was significantly increased by PLR from 47 14 mL to 50 14 mL (*p* .001), and by VE from 47 14 mL to 53 15 mL (*p* .001). The PP and VF were positively correlated with SV with, respectively, r^2 .40 (SV .69PP 5; *p* .001) and r^2 .62 (SV 1.01VF 2.4; *p* .001). Fourteen (41%) patients were considered to be responders to VE. The general characteristics of the two groups

were similar (Table 1). Within each group, hemodynamic parameters were identical at baseline 1 and baseline 2 (Table 2). The SV (17 7% vs. 4 5%; *p* .001), PP (12 8% vs. 3 6%; *p* .01), and VF (12 5% vs. 3 5%; *p* .001) were significantly higher in responders than in nonresponders, and each was positively correlated with a VEinduced increase in SV (Fig. 2).

A SV of 10% predicted fluid responsiveness with a sensitivity of 86% and a specificity of 90% (Table 3, Fig. 3). Likewise, PLR-induced increases in surrogates of SV, PP 9%, and VF 8% were able to distinguish fluid responders from nonresponders (Table 3, Fig. 3). Areas under receiver-operating characteristic curves SE for SV (area under the curve, .94 .04), PP (area under the curve, .86 .08), and VF (area under the curve, .93 .04) were not significantly different (Fig. 4).

SV at baseline (39 15 mL vs. 52 10 mL; *p* .01) and changes in SAP (9% 9% vs. 2% 3%; *p* .05) or MAP (8% 10% vs. 1% 4%; *p* .05) induced by PLR differed between responders and nonresponders. They were all tested as fluid responsiveness indices, but with lower accuracy for predicting the hemodynamic response to VE than SV, PP, or VF.

DISCUSSION

The main finding of this study was that SV, PP, and VF enabled accurate bedside prediction of preload responsiveness in nonintubated patients with severe sepsis or acute pancreatitis and can be considered interchangeable for predicting preload responsiveness. A SV of 10%, a PP of 9%, and a VF of 8% were predictive of a positive hemodynamic response to VE induced by rapid fluid infusion.

Rapid fluid loading is the usual treatment for hypovolemia. The search for predictive factors of fluid responsiveness in spontaneously breathing patients was justified, because fluid responsiveness occurred in only 41% of patients. Thus, as previously described in spontaneously breathing patients, VE does not consistently improve hemodynamics (12, 17). Interestingly, VE-induced changes in heart rate in responders and nonresponders were not different and the decrease in heart rate (2 4%; *p* .05) in responders was statistically significant but very small. Likewise, previous studies described no significant change in heart rate with VE despite a SAP increase in responder patients (12–14). Desensitizing of baroreflexes was described in patients with sepsis syndrome, septic shock, and even in healthy volunteers in a recumbent autono all in inflam

The status increas preloa ascerta determ positiv recentl fluid-l in pati (1, 2, that P with V conditi induce reversi positiv increas hemod betwee confirm rapid patient unalter activity

tem was not significantly altered. Considering its hemodynamic effects, PLR was proposed to detect responders to VE (1, 2, 25). Because SV enables prediction of VE-induced change in SV 15% with positive and negative likelihood ratios of 8.6 and .16, respectively, this study confirms that PLR effects on SV permit accurate detection of nonintubated patients who will respond positively to VE (11, 12).

To our knowledge, our study is the first to compare, in nonintubated patients, the accuracy of SV and PLRinduced changes in surrogates of SV (PP and VF) for detecting fluid responsiveness. In this particular population of patients with severe sepsis or acute pancreatitis, we did not find any difference between the

Table 2. Hemodynamic parameters at different times of the study in responders and nonresponders

	Baseline 1		PLR		Baseline 2		Post-VE	
HR, beats/min								
Nonresponders	100	23	100	24	101	24	100	23[c]
Responders	102	19	102	19	101	19	99	17[c]
SAP, mm Hg								
Nonresponders	117	23	119	22[b]	117	22	122	23[c]
Responders	109	23	118	23[b]	109	24	122	26[c]
DAP, mm Hg								
Nonresponders	59	14	60	14	60	14	62	12[c]
Responders	57	12	61	13[b]	56	11	62	12[c]
MAP, mm Hg								
Nonresponders	79	15	79	14	79	15	82	14[c]
Responders	74	13	80	14[b]	74	13	82	14[c]
PP, mm Hg								
Nonresponders	58	19	59	20	57	19	60	20[c]
Responders	53	20	58	19[b]	53	21	60	24[c]
SV, mL								
Nonresponders	52	10	54	11[b]	52	11	55	12[c]
Responders	39	15[a]	45	17[b]	40	16[a]	49	20[c]
CI, L/min/m^2								
Nonresponders	2.73	.77	2.81	.71[b]	2.75	.75	2.85	.72[c]
Responders	2.32	1.05[a]	2.70	1.21[b]	2.36	1.09[a]	2.89	1.30[c]
VF, cm/s								
Nonresponders	78	19	80	19[b]	78	19	82	21[c]
Responders	77	25	86	25[b]	78	25	90	28[c]
SV/PP								
Nonresponders	.90	.35	.92	.33	.91	.33	.92	.34
Responders	.74	.23[a]	.78	.24[b]	.75	.24[a]	.82	.25[c]
SV/VF								
Nonresponders	.67	.20	.68	.20	.67	.19	.67	.21
Responders	.51	.18[a]	.52	.19[b]	.51	.20[a]	.54	.21[c]

CI, cardiac index; PLR, passive leg raising; VE, volume expansion; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; PP, radial pulse pressure; SV, stroke volume; VF, peak velocity of femoral artery flow.

[a]*p* .05 vs. nonresponders; [b]*p* .05 vs. baseline 1; [c]*p* .05 v

accuracy of SV, PP, and VF at predicting fluid responsiveness; therefore, to this end, they can be considered as interchangeable. The use of PP and VF as preload responsiveness markers is based on the hypothesis that they depend on SV and that their relationships with SV are not altered by PLR. During each systole, the left ventricle ejects a variable amount of blood through the systemic arterial circulation. Thus, each heartbeat generates a PP wave along the arterial tree that leads to arterial blood flow (26). Both PP and VF are influenced by complex properties of the systemic arterial tree, such as compliance, wave propagation, and wave reflexion (27, 28). Previous studies demonstrated that PLR-induced changes in surrogates of SV may be used in clinical practice to predict VE responsiveness in patients with mechanical ventilation (14, 15). They also found that the use of proximal substitutes of SV, such as aortic blood flow, may be more accurate markers of fluid responsiveness than the use of more distal markers such as radial PP (14). In this study, PLR induced significant increases in SV/PP and SV/VF in responders, but not in nonresponders. However, PP and VF were significantly correlated with SV. Therefore, we conclude that the relationships between SV and its surrogates, PP and VF, are weakly but significantly altered by PLR. However, whatever the specific changes induced by PLR, PP, and VF, they were strongly correlated with the effects of VE on SV. Furthermore, PP 9% and VF 8% are able to discriminate between responders and nonresponders with very good accuracy (Table 3). Thus, physicians can choose between two devices, echo Dopp-

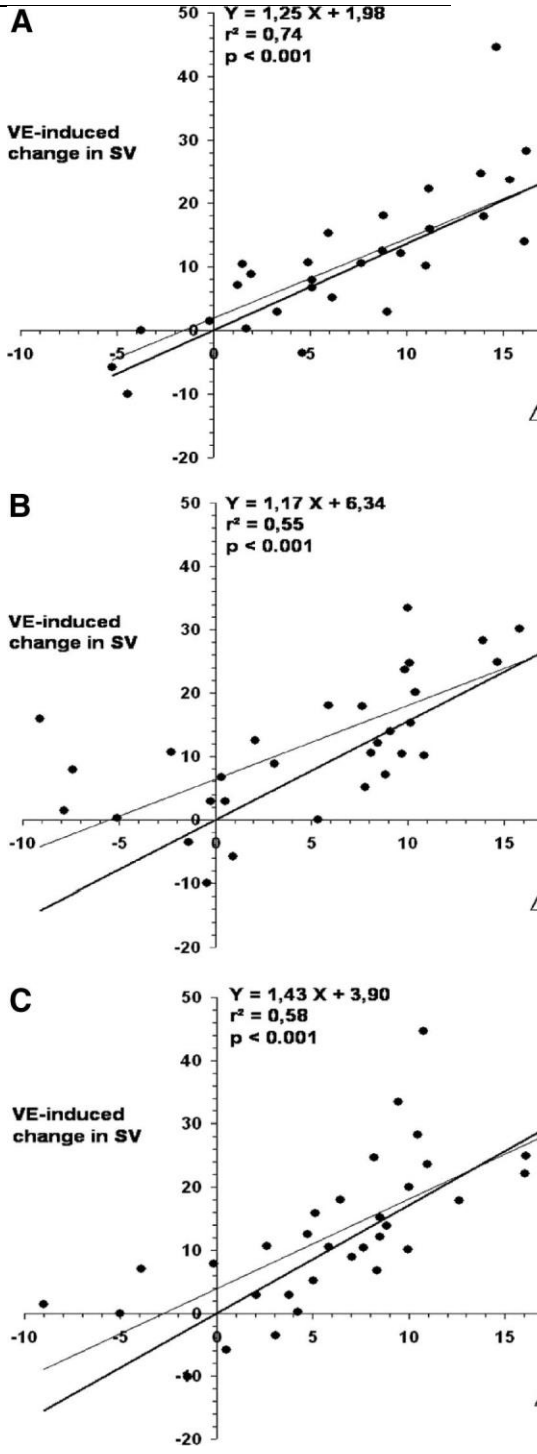


Figure 2. *A*, Linear correlation between change in stroke volumne (*SV*) induced by passive leg raising (*SV*) and volume expansion (*VE*)-induced change in stroke volume. *B*, Linear correlation between change in radial pulse pressure induced by passive leg raising (*PP*) and VE-induced change in stroke volume. *C*, Linear correlation between change in peak velocity of femoral artery flow induced by passive leg raising (*VF*) and VE-induced change in stroke volume.

ler or artery catheter, and three sites of measurement, radial artery, femoral artery, or aortic valve, to detect spontaneously breathing patients who will respond to VE. Finally, changes in SAP and MAP induced by PLR and SV at baseline were all tested as fluid-responsiveness indices, but with lower accuracy for predicting a hemodynamic response to VE than SV, PP, or VF. Because changes in SAP and MAP induced by PLR and SV at baseline are not greater than SV, PP, or VF in terms of feasibility, and because their accuracy at predicting preload responsiveness is lower, they should not be used to this end.

Attention should be directed to the specific PLR maneuver providing such results (25). Contrary to the classic PLR maneuver (9, 10, 15), this specific PLR maneuver combined trunk lowering and lower limb raising. The correlation obtained between SV and VE-induced change in SV in mechanically ventilated patients suggests that classic lower limb raising mimics a 300-mL VE (10). Given that trunk lowering may induce a 150-mL increase in intrathoracic blood volume (29), we suggest that the PLR maneuver used in our study may mimic a VE of approximately 450 to 500 mL. The correlation between SV and effects on SV induced by infusion of 500 mL 6% hydroxyethyl starch supports this hypothesis. Consequently, the threshold values for PP and VF proposed in this study to detect responders to VE may not be extrapolated to a classic PLR maneuver that might transfer a smaller amount of blood to the central compartment.

Our study has some limitations. First, it was not designed to specifically investigate physiologic effects of PLR, in particular, in terms of volume transfer and kinetics. Second, we measured SV using a modified standard left ventricular outflow track Doppler method (16). Patients were not in a lateral recumbent position, as described previously, but in a semirecumbent or PLR position. This method was previously tested (11, 12) for discriminating responders to VE in spontaneously breathing patients with low intraobserver and interobserver variabilities (12). Third, we defined the positive response to VE as an increase in SV of 15% with rapid fluid loading. This cut-off value seems clinically relevant, because it was chosen in reference to previous studies (11, 17) and was at least twice the intraobserver variability of the velocity time integral of aortic blood flow measured in this study: 2 3.7% 1.8% 7.4% 3.6%.
Fourth, echo-derived SV was used both as a predictor and as a method to measure fluid responsiveness. Therefore, accuracy of SV for predicting response to VE might be less reliable than PP or VF. To our knowledge, SV was not measured with two independent methods for predicting and measuring fluid responsiveness in previous studies. Finally, the study population comprised few or no patients with low left ventricular ejection fraction

Table 3. Accuracy of hemodynamic parameters for predicting fluid responsiveness

	Threshold Value	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
SV	10%	86%	90%	86%	90%	8.6	.16
PP	9%	79%	85%	79%	85%	5.2	.25
VF	8%	86%	80%	75%	89%	4.3	.18

SV, passive leg raising induced-change in stroke volume; PP, passive leg raising induced-change in radial pulse pressure; VF, passive leg raising induced-change in the peak velocity of femoral artery flow.

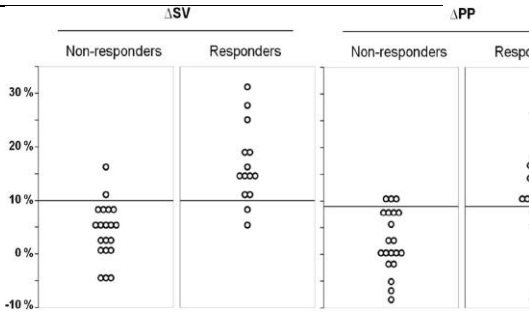
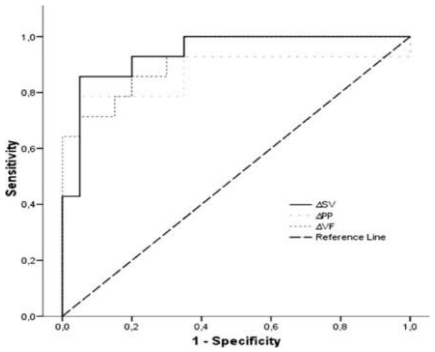


Figure 3. Individual baseline values for each indicator, passive leg raising-induced changes in stroke volume (*SV*), radial pulse pressure (*PP*), and peak velocity of femoral artery flow (*VF*) in patients with volume expansion-induced changes in SV 15% (responders) and 15%



(nonresponders).

loading responsiveness in spontaneously breathing patients with sepsis or acute pancreatitis. This finding extends the feasibility of preload responsiveness assessment by passive leg raising in spontaneously breathing patients.

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Figure 4. Receiver-operating characteristics curves comparing the capacity of changes induced by passive leg raising in stroke volume (*SV*), radial pulse pressure (*PP*), and peak velocity of femoral artery flow (*VF*) to discriminate responders from nonresponders regarding volume expansion in the overall population.

(45%) or reduced right ventricular function using vasoactive (inotropic, vasopressor, vasodilator) drugs, nonsinusal rhythm, or peripheral arterial occlusive disease. Thus, results need to be confirmed in further studies before they can be generalized to an unselected critically ill population.

CONCLUSIONS

We demonstrate that changes in left ventricular SV, radial PP, and VF are accurate and interchangeable indices of fluid- the study.

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