S100A1 in Human Heart Failure
Lack of Recovery Following Left Ventricular Assist Device Support

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Background—We hypothesized that S100A1 is regulated during human hypertrophy and heart failure and that it may be implicated in remodeling after left ventricular assist device. S100A1 is decreased in animal and human heart failure, and restoration produces functional recovery in animal models and in failing human myocytes. With the potential for gene therapy, it is important to carefully explore human cardiac S100A1 regulation and its role in remodeling.

Methods and Results—We measured S100A1, the sarcoplasmic endoplasmic reticulum Ca\(^{2+}\)ATPase, phospholamban, and ryanodine receptor proteins, as well as \(\beta\)-adrenergic receptor density in nonfailing, hypertrophied (left ventricular hypertrophy), failing, and failing left ventricular assist device–supported hearts. We determined functional consequences of protein alterations in isolated contracting muscles from the same hearts. S100A1, sarcoplasmic endoplasmic reticulum Ca\(^{2+}\)ATPase and phospholamban were normal in left ventricular hypertrophy, but decreased in failing hearts, while ryanodine receptor was unchanged in either group. Baseline muscle contraction was not altered in left ventricular hypertrophy or failing hearts. \(\beta\)-Adrenergic receptor and inotropic response were decreased in failing hearts. In failing left ventricular assist device–supported hearts, S100A1 and sarcoplasmic endoplasmic reticulum Ca\(^{2+}\)ATPase showed no recovery, while phospholamban, \(\beta\)-adrenergic receptor, and the inotropic response fully recovered.

Conclusions—S100A1 and sarcoplasmic endoplasmic reticulum Ca\(^{2+}\)ATPase, both key Ca\(^{2+}\)-regulatory proteins, are decreased in human heart failure, and these changes are not reversed after left ventricular assist device support. The clinical significance of these findings for cardiac recovery remains to be addressed.

Key Words: \(\beta\)-adrenergic beta agonists ■ calcium signaling ■ heart-assist devices ■ heart failure

Normal cardiomyocyte contraction requires precise regulation of intracellular Ca\(^{2+}\). Heart failure (HF) involves impaired Ca\(^{2+}\) handling and diminished contractile reserve due in part to altered expression and activity of Ca\(^{2+}\) regulatory proteins.1–3 Modulation of these proteins has emerged as a potential therapeutic strategy.4–6 Most recently, the CUPID (Calcium Uptregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease) trial, attempting to restore cardiomyocyte sarcoplasmic endoplasmic reticulum Ca\(^{2+}\)ATPase (SERCA) levels via gene transfer,5,8 has shown promise, further substantiating the importance of Ca\(^{2+}\) handling in myocardial recovery.

Clinical Perspective on p 618

S100A1 is a new Ca\(^{2+}\) cycling protein, emerging as a therapeutic target.11–15 S100A1 interacts with regulators of excitation–contraction coupling including SERCA, phospholamban (PLB), and ryanodine receptor (RYR).16–18 In animals, S100A1 levels correlate with disease: S100A1 is decreased in HF, while overexpression enhances contractile performance and rescues failing hearts.13,15–16,19–21 In failing human cardiomyocytes, delivery of S100A1 improves function.15 Animal studies suggest that S100A1 is required for the \(\beta\)-adrenergic response,21–23 a compensatory mechanism diminished in patients with HF.1

S100A1 expression in human HF has been studied in small cohorts of patients, postmortem or at transplant.11,15 It is important to gain understanding of S100A1 and its functional role in a large cohort of well-characterized human hearts. We tested the hypothesis that S100A1 is altered in left ventricular hypertrophy (LVH) and HF and that changes in S100A1 affect contractile function. We further investigated the relationship between S100A1 and \(\beta\)-adrenergic signaling, measuring the inotropic response to stimulation and \(\beta\)-adrenergic receptor (\(\beta\)-AR) density in the same hearts where S100A1 and other key Ca\(^{2+}\) regulatory proteins were measured.

Animal studies suggest that restoration of S100A1 levels results in recovery of cardiac structure and function in HF.19,22 We and others have shown that unloading the failing human heart with a left ventricular assist device (LVAD) results in structural and functional recovery.24–33 The effects of LVAD support on normalization of S100A1, or its potential role in LVAD-mediated recovery, have not been addressed. We tested
the hypothesis that LVAD support reverses S100A1 expression and investigated the relationship between reversal of S100A1 and that of the more traditional Ca\(^{2+}\) cycling proteins, as well as the β-adrenergic signaling pathway, both required for cardiac function.

**Methods**

**Sample Population**

We compared 4 groups: (1) hearts with normal structure and function (nonfailing [NF]); (2) hearts with left ventricular hypertrophy and preserved function (LVH); (3) hearts with cardiac failure (failing hearts [F]); and (4) hearts with cardiac failure bridged to transplant with an LVAD (F+LVAD). A secondary strategy involved a subset of the F+LVAD group, in which we made individual paired comparisons of tissue removed at LVAD implant and at transplant, in the same patients.

All tissue was obtained after informed consent, with approval of the Cleveland Clinic Institutional Review Board. NF heart tissue came from 26 unmatched organ donors with no cardiac disease and LVH tissue from 17 with preserved cardiac function and increased wall thickness. Tissue from 26 F hearts and 23 F+LVAD hearts was obtained at transplant. All F+LVAD patients were supported with the Heartmate II LVAD (Thoratec Corp). Paired samples from 11 F+LVAD hearts (a subset of the 23) were obtained at LVAD insertion (core) and transplant (Tx). Demographic and clinical data were obtained from medical records.

**Tissue Procurement**

For the F and F+LVAD groups, the entire heart was obtained in the operating room after cardioplegic arrest. The heart was immersed in cold cardioplegic solution for transport to pathology, where measurements were made and samples taken, and then the heart was taken to the laboratory, arriving within 40±10 minutes of explant. Trabecular muscles were dissected and the remaining tissue separated by chamber and frozen in liquid nitrogen for storage at −80°C. For the NF and LVH groups, hearts were procured from unused organ donors at hospitals other than Cleveland Clinic. Hearts were arrested with cardioplegic solution and transported as though used for transplant. Transport time from donor hospital to laboratory averaged 110±20 minutes. The medical chart and consent form were transported with the heart. In the laboratory, procedures were those described above.

**Muscle Function**

Contractility was measured in left ventricular trabecular muscles: 26 muscles/10 NF hearts, 9 muscles/3 LVH hearts, 39 muscles/15 F hearts, and 53 muscles/14 F+LVAD hearts for group comparisons. For paired LVAD core/Tx comparisons, 59 muscles/8 hearts were used (including 27 muscles from 8 cores and 32 muscles from the same 8 hearts at explant). When the whole heart was available, muscles were dissected from the left ventricular free wall, close to the apex. From the apical core, muscles were dissected from the endocardial surface. Muscles in the core were fewer in number than those in the free wall, but there were sufficient muscles to study 2 or 3 per core, and they were similar in appearance, size, shape, and function to free wall muscles. Muscles were studied in a tissue bath filled with Krebs–Henseleit solution at 37°C, as described, and were stimulated through parallel platinum electrodes in contact with the muscle surface. Stimulation was delivered at 1.0 Hz, 5-ms duration, and 20% above threshold. Length–tension curves were generated, beginning at a resting tension of 0.5 to 1.0g and continuing for cardiac function.

β-adrenergic signaling pathway, both required as well as the

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**Results**

Table 1 shows patient information for the 4 groups. Groups were similar in age range, sex, and race, although the F+LVAD group was slightly older than the NF group. The F and F+LVAD groups contained roughly equal numbers of dilated and ischemic etiologies. Left ventricular ejection fraction was normal in NF and LVH groups. LVAD duration was equal in the F+LVAD group and the subset available for paired comparisons.

S100A1 did not change in LVH but was decreased in F compared with NF (P<0.05; Figure 1A). S100A1 levels did not recover after LVAD support (P<0.01 versus NF; Figure 1A). Like S100A1, SERCA was also preserved in LVH, significantly decreased in F (P<0.001), but failed to show recovery after LVAD (P>0.001 versus NF; Figure 1B). PLB also did not change in LVH and was decreased in F (P<0.05), but PLB showed full recovery after LVAD support (Figure 1C). RYR protein did not differ from NF in LVH, F, or F+LVAD hearts (Figure 1D). In this small sample, there were no differences in S100A1 according to cause of HF (dilated cardiomyopathy=1.39±0.18 relative densitometric units [RDU] versus ischemic cardiomyopathy=1.36±0.21 RDU; P=0.52) or sex (NF men=1.62±0.21 RDU versus NF women=1.98±0.15 RDU; P=0.19; and F men=1.36±0.21 RDU versus F women=1.38±0.18 RDU; P=0.66).

Figure 1 compares the 4 groups of patients, assessing the effect of LVAD support by comparing patients who were supported by LVAD to those who were not. The effects of LVAD can also be determined by comparing paired samples from the
same hearts before and after LVAD, which we did in a subset of 11 of the original 23 F+LVAD hearts. This approach confirmed the conclusion that LVAD support failed to normalize either S100A1 or SERCA, but did normalize PLB protein (Figure 2).

LVAD duration had no effect on S100A1 or SERCA. In the same hearts, we investigated the functional consequences of alterations in proteins responsible for contractile regulation, by measuring baseline and stimulated muscle contractility, as described.32–35 Baseline developed tension at Lmax did not differ in muscles from LVH, F, or F+LV AD compared with NF (Figure 3). The remaining 5 isometric contractile parameters also did not differ between groups (Table 2) and did not change from LV AD implant (core) to LV AD explant (Tx; Table 2).

In addition to baseline contractility, we measured the response to stimulation with a single dose of 1 μmol/L isoproterenol, a β-adrenergic agonist. Response to β-adrenergic stimulation is vital for normal cardiac function, is compromised in HF,33,36,38 and has been postulated to depend on the presence of S100A1.21–23 As observed in Figure 4A, the inotropic response to isoproterenol was significantly decreased in muscles from F compared with NF (P<0.001), but the response recovered after LVAD support. Muscle function data were available from 8 of the original 11 F+LVAD pairs, and these data confirmed recovery of the inotropic response (Figure 4B).

To further investigate the relationship between S100A1 and β-adrenergic signaling, we measured β-AR density in the same hearts, which had been used for all previous measurements. Figure 5 shows no effect of LVH on β-AR, but a significant decrease in receptor density in F compared with NF (P<0.01) and recovery of β-AR after LVAD.

**Discussion**

**S100A1 in Human HF**

We used a large sample of well-characterized F and NF human hearts to confirm that the Ca2+ regulatory protein S100A1 was decreased in human HF, similar to what has been shown for other proteins involved in intracellular Ca2+ regulation1–3 and for S100A1 in smaller studies.11,15 This was important because studies in animals and in human cardiac cells have shown that restoring S100A1 expression reverses the HF phenotype,5,13,15,17,18,20,21,23 suggesting therapeutic potential. We found no evidence for differential regulation of

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**Table 1. Patient Information**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age* (Years)</th>
<th>Sex (M/F)</th>
<th>Race (W/B)</th>
<th>Diagnosis (DCM/ICM)</th>
<th>LVEF* (%)</th>
<th>LVAD Support* Duration (Days)</th>
<th>Medications†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF</td>
<td>26</td>
<td>47±12</td>
<td>11/15</td>
<td>25/1</td>
<td>NA</td>
<td>61±7</td>
<td>NA</td>
<td>INO</td>
</tr>
<tr>
<td>LVH</td>
<td>17</td>
<td>51±10</td>
<td>11/6</td>
<td>16/1</td>
<td>NA</td>
<td>56±15</td>
<td>NA</td>
<td>INO</td>
</tr>
<tr>
<td>Failing</td>
<td>26</td>
<td>52±9</td>
<td>13/13</td>
<td>22/4</td>
<td>13/13</td>
<td>15±4‡</td>
<td>NA</td>
<td>ACE-I, INO</td>
</tr>
<tr>
<td>F+LVAD§</td>
<td>23</td>
<td>55±15¶</td>
<td>19/4</td>
<td>21/2</td>
<td>12/11</td>
<td>16±5‡</td>
<td>168±105</td>
<td>AA, ACE-I, BB</td>
</tr>
<tr>
<td>LVAD pairs§</td>
<td>11</td>
<td>56±14</td>
<td>9/2</td>
<td>10/1</td>
<td>6/5</td>
<td>15±3</td>
<td>162±86</td>
<td>AA, ACE-I, BB</td>
</tr>
</tbody>
</table>

AA indicates antiarrhythmic; ACE-I, angiotensin-converting enzyme inhibitor; B, black; BB, β-adrenergic receptor blocker; DCM, dilated cardiomyopathy; F, female; F+LVAD, failing heart supported by left ventricular assist device; ICM, ischemic cardiomyopathy; INO, inotrope; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; M, male; NA, not applicable; NF, nonfailing; and W, white.

*Age, LVEF, and LVAD support duration are expressed as mean±SD.
†≥50% of the patients were prescribed a drug from this classification.
‡P<0.001 vs NF.
§Information on LVAD-supported patients reflects transplant time point.
¶P<0.05 vs NF.
Lack of Recovery of S100A1 After LVAD Support

S100A1 based on HF diagnosis or sex in this small sample. We also showed that S100A1 was not decreased in hearts with LVH, suggesting that downregulation occurs later during progression to HF, as shown for SERCA and PLB. Although S100A1 was decreased in right ventricular hypertrophy in pigs, our data suggest a lack of regulation in human LVH.

Data from any study of human heart tissue depend on careful tissue procurement and sufficient numbers for group matching. The hearts in our tissue bank have been procured by the same team using the same methods for 25 years. Protocols were designed to decrease transport time and minimize warm ischemic time. For this study, we matched the NF, F, and LVH groups for age, sex, and race, we chose equal numbers of F hearts with dilated cardiomyopathy and ischemic cardiomyopathy, and we excluded long ischemic times. Differences in transport time between organ donors at other institutions (NF and LVH) and transplant patients in our operating rooms (F and F+LVAD) are inevitable, but evidence suggests that group differences in S100A1 protein were not related to tissue procurement. Transport times were less than the 4-hour window which is allowed between organ harvest and transplantation, and muscle function was within normal limits for all hearts. If longer transport time in NF and LVH hearts caused increased ischemia or proteolysis, we would expect all proteins to be decreased in those hearts. In this, as well as our previous studies, some proteins did not differ between groups (RYR), and in the current study, S100A1, SERCA, and PLB were lower in F hearts, suggesting that the increased transport time for NF and LVH hearts did not decrease protein levels through degradation.

S100A1 After LVAD Support

Studies in animals and more recently in human cardiac myocytes show that increasing S100A1 overcomes Ca cycling deficits and contractile abnormalities. We hypothesized that recovery of S100A1 might participate in cellular remodeling after LVAD, but data failed to support that hypothesis. Although we and others have previously shown that LVAD support normalizes cellular and molecular changes associated with HF, and we show here that PLB is normalized (Figures 1 and 2), data demonstrate that both S100A1 and SERCA failed to recover after Heartmate II (HMII) support (Figures 1 and 2). This observation was confirmed using 2 methods, the group comparison (F+LVAD versus NF versus F hearts) and the paired comparison (core- versus Tx-matched samples from the same patients), lending rigor to the analysis and leading us to conclude that there is no change in these 2 proteins after HMII. Further analysis showed no effects of support duration and no confounding changes in medications after LVAD implant. Our earlier study demonstrated reversal of SERCA after LVAD. That study was conducted with an earlier generation, pulsatile flow LVAD, and our current results fail to show the same recovery with the newer, continuous flow LVAD.

Effects of S100A1 on Muscle Function

As shown previously, baseline muscle contraction was normal in muscles taken from F or LVH and did not change after LVAD (Table 2; Figure 3). Although S100A1, SERCA, and PLB are involved in excitation–contraction coupling, decreases of the magnitude observed were not sufficient to produce decreased baseline contractile function. It is possible that S100A1’s role is specifically in the regulation of contractile reserve and evident only with increased workload. S100A1 knockout mice show normal muscle contraction but an impaired response to β-adrenergic stimulation. Figure 4A shows the same for human F. β-Adrenergic stimulation produces less inotropy in F heart muscles than NF muscles. The inotropic response recovers after LVAD.
Table 2. Isometric Contractility of Left Ventricular Trabecular Muscles at Lmax

<table>
<thead>
<tr>
<th></th>
<th>NF</th>
<th>LVH</th>
<th>Failing</th>
<th>F+LVAD</th>
<th>Core</th>
<th>F+LVAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (muscles/hearts)</td>
<td>26/10</td>
<td>9/3</td>
<td>39/15</td>
<td>53/14</td>
<td>27/8</td>
<td>36/8</td>
</tr>
<tr>
<td>RT, g/mm²</td>
<td>2.54±1.56</td>
<td>1.76±1.05</td>
<td>2.88±1.34</td>
<td>3.03±1.36</td>
<td>3.59±1.13</td>
<td>3.20±1.64</td>
</tr>
<tr>
<td>DT, g/mm²</td>
<td>1.19±0.59</td>
<td>1.73±0.79</td>
<td>1.17±0.63</td>
<td>1.23±0.48</td>
<td>1.70±0.45</td>
<td>1.17±0.52</td>
</tr>
<tr>
<td>TPT, ms</td>
<td>176.5±25.2</td>
<td>169.3±10.1</td>
<td>162.5±30.9</td>
<td>197.5±18.2</td>
<td>174.3±18.7</td>
<td>198.4±20.3</td>
</tr>
<tr>
<td>THR, ms</td>
<td>135.1±12.6</td>
<td>141.3±8.1</td>
<td>147.5±15.6</td>
<td>134.4±11.3</td>
<td>131.4±19.4</td>
<td>134.5±11.2</td>
</tr>
<tr>
<td>+dT/dt, g/s per mm²</td>
<td>9.22±3.51</td>
<td>13.80±5.79</td>
<td>11.09±5.31</td>
<td>8.60±2.93</td>
<td>13.96±3.66</td>
<td>8.24±3.25</td>
</tr>
<tr>
<td>−dT/dt, g/s per mm²</td>
<td>7.90±3.15</td>
<td>11.61±5.00</td>
<td>9.00±4.41</td>
<td>7.51±2.93</td>
<td>10.63±2.47</td>
<td>7.19±2.95</td>
</tr>
</tbody>
</table>

Data expressed as mean±SD. +dT/dt indicates maximum rate of tension rise; −dT/dt, maximum rate of tension fall; DT, developed tension; F+LVAD, failing human heart supported by a left ventricular assist device; LVH, left ventricular hypertrophy; n, number of muscles/number of hearts; NF, nonfailing; RT, resting tension; THR, time to half relaxation; and TPT, time to peak tension.

(4A and 4B). S100A1 is not essential for recovery of the β-adrenergic response, and, if S100A1 plays a regulatory role in this signaling pathway, either the decreased S100A1 observed in human HF is not sufficient to impair the response or compensatory mechanisms are recruited.

We have previously shown that both the inotropic response and β-AR recovered after pulsatile LVAD.33 In the current study, we showed that recovery of the inotropic response is also accompanied by recovery of β-AR after continuous flow LVAD (Figure 5). Animal studies have suggested that S100A1 is necessary for the β-adrenergic inotropic response,21–23 but our data argue against that relationship in the human heart because S100A1 did not recover in the same hearts where β-AR responsiveness was restored. We should note that patients in the F+LVAD group were frequently taking β-blockers (Table 1), both at the time of LVAD implant and at the time of transplant, but the use of β-blocker therapy in this population was not associated with any change in the inotropic response or β-AR density in our study.

S100A1 and LVAD Type

Although ours is the first report of S100A1 levels after LVAD, previous studies have suggested that other elements of the HF phenotype including SERCA and β-AR receptors and response return to NF levels. These studies have been done with tissue from patients supported by the earlier generation, pulsatile flow LVAD.32,33,40–42,44 In our current study, while recovery of the β-adrenergic response, β-AR, and PLB was demonstrated, SERCA failed to show recovery with Heartmate II LVAD, as did S100A1. Some studies comparing the 2 types of LVAD have reported equal unloading and hemodynamics,45–48 while others have suggested that the pulsatile LVADs produce greater unloading.49,50 result in more recovery, and allow more device removal.49 Few studies have examined molecular and cellular changes after the newer, continuous flow LVADs. Thohan et al46 showed greater unloading with the pulsatile LVAD but reported similar changes in cytokines, collagen, and cell size with the continuous flow LVAD. Ambardekar et al51 reported similar remodeling produced by the older versus newer LVADs, although their small sample size may have limited statistical power. Our study does not directly compare LVADs with pulsatile versus continuous flow, so we cannot conclude that the recovery of SERCA in our earlier study32 and lack of recovery in the current study are related to LVAD type. It is clear,

Figure 4. Functional response to β-adrenergic stimulation. Inotropic response to 1 μmol/L isoproterenol (A). Muscles are taken from the same hearts used for protein analysis and are the same muscles from which baseline muscle function was recorded. Comparison includes nonfailing (NF; 26 muscles/10 hearts), left ventricular hypertrophy (LVH; 4 muscles/2 hearts), failing (F; 39 muscles/15 hearts), and failing human heart supported by a left ventricular assist device (F+LVAD; 53 muscles from 14 hearts; *P<0.05, **P<0.001 vs NF). B, Paired muscles from 8 of the 11 pairs of F+LVAD samples, muscles removed at LVAD implant (Core; n=27 muscles from 8 hearts), and explant (Tx; n=32 muscles from the same 8 hearts). *P<0.05 vs Core. Nonsignificant P values vs NF: (A) LVH P=0.91, F+LVAD P=0.28.

Figure 5. β-Adrenergic receptor (β-AR) density. Total β-AR in the same nonfailing (NF; n=9), left ventricular hypertrophy (LVH; n=7), failing (F; n=15), and failing human heart supported by a left ventricular assist device (F+LVAD; n=14) hearts used for protein analysis and muscle function studies. **P<0.01 vs NF. Nonsignificant P values vs NF: LVH P=0.50, F+LVAD P=0.43.
however, that in the current study, HMII failed to reverse both SERCA and S100A1. Both proteins are important for cardiac excitation–contraction coupling. The clinical significance of these findings, as they relate to recovery after LVAD support of the failing human heart, remains to be determined.

**Limitations**

Studies of human heart tissue are limited by the inability to control important variables between patients and groups and difficulty normalizing for baseline differences because tissue is mainly available at transplant. This is mitigated in the LVAD population, where paired samples can be studied, but this is not always possible. Even with these limitations, however, studies such as these provide vital information on human HF and reversibility in cases where therapeutic potential exists and gene therapy is on the horizon.

**Acknowledgments**

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**Disclosures**

None.

**References**


Cirrhosis of the liver

July 2014

618


CLINICAL PERSPECTIVE

Patients with end-stage heart failure are often supported until transplantation with a left ventricular assist device (LVAD). LVADs are also approved as destination therapy for those who may not be candidates for transplantation. Many studies have documented clinical improvement in patients with LVAD support, and laboratory investigations have shown remodeling of many cellular and molecular elements of the heart failure phenotype. In spite of clinical improvement and cellular remodeling, however, the LVAD does not reproducibly improve the failing heart enough to cause sustained patient improvement and make transplantation unnecessary. This fact has led physicians and scientists to think that there may be some element of clinical recovery or cellular remodeling after LVAD that is limiting or incompletely understood. In this article, we report on our studies of S100A1, a calcium-cycling protein whose importance for cardiac function is well enough established that gene therapy trials are being proposed. Yet S100A1 did not recover with LVAD support in our study. Importantly, sarcoplasmic endoplasmic reticulum Ca2+-ATPase, another key calcium regulatory protein, also did not recover in this study, where patients were supported until transplant with the newer generation continuous flow LVAD. Work by us and others has previously shown recovery of sarcoplasmic endoplasmic reticulum Ca2+-ATPase with older pulsatile pumps. This study is important because it suggests that cellular remodeling of the failing heart after currently available LVAD support may be incomplete. If some key regulatory proteins do not recover, this may help in understanding why functional recovery sufficient to enable removing LVAD support is so infrequent.
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